Circulation Journal
Circ J 2021; 85: 402–572
doi:10.1253/circj.CJ-19-1131



# JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases

Masakazu Yamagishi; Nagara Tamaki; Takashi Akasaka; Takanori Ikeda; Kenji Ueshima; Shiro Uemura; Yutaka Otsuji; Yasuki Kihara; Kazuo Kimura; Takeshi Kimura; Yoshiki Kusama; Shinichiro Kumita; Hajime Sakuma; Masahiro Jinzaki; Hiroyuki Daida; Yasuchika Takeishi; Hiroshi Tada; Taishiro Chikamori; Kenichi Tsujita; Kunihiko Teraoka; Kenichi Nakajima; Tomoaki Nakata; Satoshi Nakatani; Akihiko Nogami; Koichi Node; Atsushi Nohara; Atsushi Hirayama; Nobusada Funabashi; Masaru Miura; Teruhito Mochizuki; Hiroyoshi Yokoi; Kunihiro Yoshioka; Masafumi Watanabe; Toshihiko Asanuma; Yuichi Ishikawa; Takahiro Ohara; Koichi Kaikita; Tokuo Kasai; Eri Kato; Hiroshi Kamiyama; Masaaki Kawashiri; Keisuke Kiso; Kakuya Kitagawa; Teruhito Kido; Toshio Kinoshita; Tomonari Kiriyama; Teruyoshi Kume; Akira Kurata; Satoshi Kurisu; Masami Kosuge; Eitaro Kodani; Akira Sato; Yasutsugu Shiono; Hiroki Shiomi; Junichi Taki; Masaaki Takeuchi; Atsushi Tanaka; Nobuhiro Tanaka; Ryoichi Tanaka; Takuya Nakahashi; Takehiro Nakahara; Akihiro Nomura; Akiyoshi Hashimoto; Kenshi Hayashi; Masahiro Higashi; Takafumi Hiro; Daisuke Fukamachi; Hitoshi Matsuo; Naoya Matsumoto; Katsumi Miyauchi; Masao Miyagawa; Yoshitake Yamada; Keiichiro Yoshinaga; Hideki Wada; Tetsu Watanabe; Yukio Ozaki; Shun Kohsaka; Wataru Shimizu; Satoshi Yasuda; Hideaki Yoshino
on behalf of the Japanese Circulation Society Working Group

## Table of Contents



J-STAGE Advance Publication released online February 16, 2021

This English document is a revised version of JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases reported at the Japanese Circulation Society Joint Working Group performed in 2019 (https://www.j-circ.or.jp/cms/wp-content/uploads/2020/02/JCS2018_yamagishi_tamaki.pdf). In this version, some content and references have been modified in accordance with advances in the latest information of each area.

Refer to **Appendix 1** for the details of members.

Joint Working Groups: Japanese Circulation Society, Japan Radiological Society, Japanese Society of Nuclear Medicine, Japanese Society of Medical Imaging, Japanese Coronary Association, Japanese Society of Pediatric Cardiology and Cardiac Surgery, Japanese Society of Echocardiography, Japanese Association of Cardiovascular Intervention and Therapeutics, Japanese Society of Cardiovascular Imaging & Dynamics, Japanese Society of Nuclear Cardiology, Japan College of Cardiology, Japan Society of Ultrasonics in Medicine, Japan Atherosclerosis Society, Japanese Heart Rhythm Society, and Japanese College of Angiology.

Mailing address: Guideline Committee of the Japanese Circulation Society, 6th Floor, Uchikanda Central Building, 1-18-13 Uchikanda, Chiyoda-ku, Tokyo 101-0047, Japan. E-mail: jcsGL@j-circ.or.jp



ISSN-1346-9843

## Abbreviations

| | |
|---|---|
| ABI | ankle–brachial index |
| ACC | American College of Cardiology |
| ACS | acute coronary syndrome |
| AHA | American Heart Association |
| APV | averaged peak velocity |
| ARH | autosomal recessive hypercholesterolemia |
| AS | Agatston score |
| ASO | arteriosclerosis obliterans |
| ATP | adenosine triphosphate |
| BMIPP | $\beta$-methyl-p-iodophenyl-pentadecanoic acid |
| BNP | B-type natriuretic peptide |
| CABG | coronary artery bypass grafting |
| CACS | coronary artery calcium score |
| CAD | coronary artery disease |
| CANM | Canadian Association of Nuclear Medicine |
| CanSCMR | Canadian Society of Cardiovascular Magnetic Resonance |
| CAR | Canadian Association of Radiologists |
| CCS | Canadian Cardiovascular Society |
| CCTA | coronary CT angiography |
| CDC | Centers for Disease Control and Prevention |
| CFR | coronary flow reserve |
| CFVR | coronary flow velocity reserve |
| CI | confidence interval |
| CKD | chronic kidney disease |
| CNCS | Canadian Nuclear Cardiology Society |
| CPAP | continuous positive airway pressure |
| CT | computed tomography |
| CTA | computed tomography angiography |
| CTDIvol | computed omography dose index volume |
| DES | drug-eluting stent |
| DLP | dose–length product |
| ECG | electrocardiography |
| EDV | end-diastolic volume |
| eGFR | estimated glomerular filtration rate |
| ESC | European Society of Cardiology |
| ESV | end-systolic volume |
| FBP | filtered back projection |
| FDA | Food and Drug Administration |
| FDG | fluorodeoxyglucose |
| FDG-PET | fluorodeoxyglucose–positron emission tomography |
| FFR | fractional flow reserve |
| FFR-CT | CT-derived fractional flow reserve |
| FH | familial hypercholesterolemia |
| 1/3FR mean | one-third mean filling rate |
| GLS | global longitudinal strain |
| ICD | implantable cardioverter defibrillator |
| iFR | instantaneous wave-free ratio |
| IMT | intima–media thickness |
| IVUS | intravascular ultrasound |
| LDL | low-density lipoprotein |
| LGE | late gadolinium enhancement |
| LP | late potential |
| LVEF | left ventricular ejection fraction |
| MACE | major adverse cardiovascular events |
| MDCT | multidetector [row] CT |
| MIBI | methoxy-isobutyl isonitrile |
| MRA | magnetic resonance angiography |
| MRI | magnetic resonance imaging |
| M-TWA | microvolt ($\mu$V)–T wave alternans |
| NSF | nephrogenic systemic fibrosis |
| NURD | non-uniform rotational distortion |
| OCT | optical coherence tomography |
| OMI | old (previous) myocardial infarction |
| PAD | peripheral arterial disease |
| PCI | percutaneous coronary intervention |
| PESP | postextrasystolic potentiation |
| PET | positron emission tomography |
| PFR | peak filling rate |
| QCA | quantitative coronary angiography |
| QOL | quality of life |
| RCT | randomized controlled trial |
| SAE | signal-averaged ECG |
| SPECT | single photon emission computed tomography |
| TCFA | thin-cap fibroatheroma |
| TBI | toe–brachial index |
| Tc | technetium |
| TOF | time-of-flight |
| TPF | time-to-peak filling |
| TWA | T-wave alternans |

## Introduction

There have been remarkable advances in the methods used for diagnosis and clinical evaluation of cardiovascular diseases. Noninvasive diagnostic techniques have developed to unprecedented levels over the past decade, particularly those using CT, MRI, radioisotope (RI) imaging, and echocardiography. Intravascular imaging was initiated as IVUS, and there has been significant progress in the field of functional evaluation as well as morphological evaluation.

The first edition of this Guideline was released in 1998–99 to provide an overview of the wide variety of examinations available for coronary heart diseases and the status of each examination at that time. The Guideline was subsequently revised in 2005 and 2010 as Guidelines for Diagnostic Evaluation of Patients with Chronic Ischemic Heart Diseases to incorporate new advances in testing. In addition to this area, the Guideline has undergone substantial revision based on the JCS 2010 Guidelines for Clinical Use of Cardiac Nuclear Medicine[1] and the JCS 2009 Guidelines for Noninvasive Diagnosis of Coronary Artery Lesions.[2]

This revised version has 3 parts, which cover the information provided in the first version and the previous revised versions, as well as risk assessment. Chapter I covers the "**Significance of Various Tests for Diagnosis of Chronic Coronary Heart Disease**", and describes the characteristics and technical aspects of each test, as well as the conditions for which each test is useful. Chapter II – "**Risk Assessment and Management**" – has been newly added in this version. Chapter III, "**Selecting Tests for Chronic Coronary Heart Disease Based on the Pathological Condition and Diagnostic Objectives**", explains how to select and use various test methods for evaluating disease states, the prognosis, and the effects of treatment. References to the literature published since 2010 have been added during the preparation of this Guideline. Data obtained in Japan were reviewed whenever possible. Some information about acute myocardial infarction and unstable angina has been excluded because separate guidelines are available for these conditions.

This Guideline is designed to assist clinicians, especially cardiologists, diagnose chronic coronary heart disease, evaluate its severity, formulate a treatment plan, assess the response to treatment, and manage patients. In particular, the characteristics and diagnostic performance of each test are explained, as well as how effective each test is for different diagnostic purposes and disease states, together with the potential pitfalls. In addition, this Guideline is intended to provide support for selecting a combination of multiple tests so that the information required to treat individual patients can be obtained. For this reason, the "Level of evidence", which indicates the relationship between each test/diagnosis and clinical outcomes, is also mentioned whenever possible, although it can be difficult to establish evidence for such relationships. Accordingly, this Guideline may also be useful for other healthcare professionals in addition to clinicians. We hope this Guideline will be a source of useful information in hospital wards, outpatient clinics, and laboratories.

## Recommendations and Levels of Evidence

In this Guideline, the recommendations and levels of evidence are classified in accordance with recent guidelines of the Japanese Circulation Society, the ACC/AHA, and the ESC (**Tables 1**,**2**). These guidelines are already widely used, so adopting the same classification facilitates comparison between Japanese and overseas guidelines.

In Japan, the recommendation grades and levels of evidence proposed by the Medical Information Network Distribution Service (MINDS), a medical information service of the Japan Council for Quality Health Care, have recently been widely adopted (**Tables 3**,**4**).[3] The MINDS Guide for Developing Clinical Practice Guidelines 2007[3] provides a classification framework that is slightly different from the conventional recommendation grades/levels of evidence, with the MINDS classification being more oriented towards tests and research.

Because these classifications are useful, both are included in this Guideline whenever possible. The recommendations presented herein were first determined by the individual authors based on the literature published in Japan and overseas, and then were assessed by peer review in meetings of Study Group members and the External Evaluation Committee.

**Table 1. Classes of Recommendations**

| | |
|---|---|
| Class I | Evidence and/or general agreement that a given procedure or treatment is useful and effective |
| Class II | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given procedure or treatment |
| Class IIa | Weight of evidence/opinion is in favor of usefulness/efficacy |
| Class IIb | Usefulness/efficacy is less well established by evidence/opinion |
| Class III | Evidence or general agreement that the given procedure or treatment is not useful/effective, and in some cases may be harmful |

**Table 2. Levels of Evidence**

| | |
|---|---|
| Level A | Data derived from multiple randomized clinical trials or meta-analyses |
| Level B | Data derived from a single randomized clinical trial or large-scale nonrandomized studies |
| Level C | Consensus of opinion of the experts and/or small-size clinical studies, retrospective studies, and registries |

| Table 3. MINDS Grades of Recommendations | |
|---|---|
| Grade A | Strongly recommended and supported by strong evidence |
| Grade B | Recommended with moderately strong supporting evidence |
| Grade C1 | Recommended despite no strong supporting evidence |
| Grade C2 | Not recommended because of the absence of strong supporting evidence |
| Grade D | Not recommended as evidence indicates that the treatment is ineffective or even harmful |

(Reproduced from MINDS handbook in practical guideline 2007. Tokyo: Igakushoin, 2007; 16.[3])

| Table 4. MINDS Levels of Evidence (Levels of Evidence in Literature on Treatment) | |
|---|---|
| I | Systematic review/meta-analysis of randomized controlled trials |
| II | One or more randomized controlled trials |
| III | Nonrandomized controlled trials |
| IVa | Analytical epidemiological studies (cohort studies) |
| IVb | Analytical epidemiological studies (case-control studies and cross-sectional studies) |
| V | Descriptive studies (case reports and case series) |
| VI | Not based on patient data, or based on opinions from a specialist committee or individual specialists |

(Reproduced from MINDS handbook in practical guideline 2007. Tokyo: Igakushoin, 2007; 15.[3])

## Pretest Probability and Cardiovascular Risk

This Guideline describes and provides guidance on the Significance of Various Tests for Diagnosis of Chronic Coronary Heart Disease, Risk Assessment and Management, and Selecting Tests for Chronic Coronary Heart Disease Based on the Pathological Condition and Diagnostic Objectives. The pretest probability for each test is listed as low (<30%), medium (≥30 and <70%), or high (≥70%).

Cardiovascular risk is described in accordance with the classification in the Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017[4] from the Japan Atherosclerosis Society, which defines the expected risk of developing coronary heart disease in a 10-year period as low (<2%), medium (≥2 and <9%), or high (≥9%).

However, because some of the literature classifies those risks by different criteria, separate descriptions are provided in such cases.

## I. Significance of Various Tests for Diagnosis of Chronic Coronary Heart Disease

### 1. Exercise Electrocardiography

The most important purpose of exercise ECG is to diagnose coronary heart disease. Electrocardiography assesses the electrical activity of the myocardium and thus reflects myocardial ischemia, so whether exercise produces ischemic changes on the electrocardiogram is investigated. Determining myocardial ischemia indicates the presence of functional coronary stenosis. Accordingly, exercise ECG is complementary to coronary angiography, which provides a morphological evaluation of coronary artery stenosis. In addition to diagnosing coronary heart disease, ECG is also used for follow-up after coronary revascularization, preoperative examination before noncardiac surgery in patients with coronary heart disease, cardiac rehabilitation, and prescription of exercise for lifestyle-related diseases. In the USA and Europe, the Duke treadmill score is used to predict the long-term prognosis.[5]

#### 1.1 Sensitivity and Specificity

The sensitivity and specificity of exercise ECG for detecting coronary artery stenosis are approximately 75% and 70%, respectively,[6–10] and the pretest probability for an individual patient should also be taken into consideration.[6] Pretest probability is related to the percentage of persons with the target disease in a particular population. In populations with a high prevalence of coronary heart disease, such as older men with multiple coronary risk factors and typical angina pain, the probability of coronary heart disease existing (a true-positive result) is very high if exercise ECG is positive. Moreover, even if ECG is negative, there is the possibility of a false-negative result. Conversely, even if exercise ECG is positive in persons from a young or middle-aged population, they often have normal coronary arteries (a false-positive result). Clinicians should decide on the next diagnostic step by comprehensive evaluation, together with assessment of whether exercise ECG is positive or negative.

#### 1.2 Indications and Contraindications

In addition to making a definitive diagnosis of suspected coronary heart disease, exercise ECG can be used for screening high-risk patients and for follow-up of patients with coronary heart disease after coronary revascularization or during drug therapy. Each of these uses will be detailed in the itemized discussion.

Contraindications to this test include acute myocardial

| Table 5. Contraindications of Exercise Stress Testing |
|---|
| **Absolute contraindications** |
| ① Acute myocardial infarction, unstable angina |
| ② Uncontrolled arrythmia |
| ③ Symptomatic severe aortic valve stenosis |
| ④ Acute or severe heart failure |
| ⑤ Acute pulmonary embolism or lung infarction |
| ⑥ Acute myocarditis or pericarditis |
| ⑦ Aortic dissection or aneurysm |
| **Relative contraindications** |
| ① Left main stenosis |
| ② Moderate aortic valve stenosis |
| ③ Severe electrolytic abnormality |
| ④ Severe hypertension |
| ⑤ Tachyarrhythmia or bradyarrhythmia |
| ⑥ Obstructive hypertrophic cardiomyopathy |
| ⑦ Mental and physical disturbance which cannot exercise |
| ⑧ Advanced atrioventricular block |

(Reproduced from Fletcher et al 2013,[11] with permission.)

| Table 6. Bruce Protocol | | | |
|---|---|---|---|
| Stage (each 3 min) | Speed mile/h (km/h) | Slope (%) | Estimate METs |
| 1 | 1.7 (2.7) | 10 | 4.8 |
| 2 | 2.5 (4.0) | 12 | 6.8 |
| 3 | 3.4 (5.5) | 14 | 9.6 |
| 4 | 4.2 (6.9) | 16 | 13.2 |
| 5 | 5.0 (8.0) | 18 | 16.6 |
| 6 | 5.5 (8.8) | 20 | 20.0 |
| 7 | 6.0 (9.6) | 22 | – |

(Reproduced from Bruce et al 1963,[16] with permission.)

| Table 7. Criteria for Exercise Cancellation |
|---|
| **Subjective symptoms** |
| Subject requests to cancel |
| Mild chest pain with ST depression |
| Moderate chest pain without ST depression |
| Dyspnea, leg fatigue, general fatigue |
| [Equivalent to 17 of Borg score[19]] |
| **Objective findings** |
| Wandering, waxing, ataxia, pale |
| Cyanosis, nausea |
| Yawning, other peripheral circulatory failure |
| **ST change** |
| ST depression (>0.1 mV horizontal, downsloping) |
| ST elevation (>0.1 mV) |
| **Arrhythmia** |
| Ventricular tachycardia |
| R on T phenomenon |
| Continuous ventricular bigeminy, trigeminy |
| 30% or more premature ventricular contractions |
| Continuous supraventricular tachycardia and atrial fibrillation |
| II or III degree atrioventricular block |
| **Blood pressure response** |
| Excessive rise of blood pressure (systolic blood pressure >250 mmHg, diastolic blood pressure >120 mmHg) |
| Decrease in blood pressure (>10 mmHg decrease during exercise or if it does not rise) |
| **Heart rate response** |
| 85–90% of predicted maximum heart rate, abnormal bradycardia |
| **Others** |
| ECG or blood pressure monitor does not work properly |

(Reproduced from Saito M, 1993,[17] and American College of Sports Medicine, 1986,[18] with permission.)

infarction and severe valvular disease, because exercise aggravates these conditions (**Table 5**).[11] The AHA guideline states that exercise ECG can be performed in patients with suspected unstable angina, providing that the risk is deemed to be low based on pretest evaluation.[12] In patients with secondary ST changes, such as Wolff-Parkinson-White syndrome (WPW syndrome) or left bundle branch block, the diagnosis of coronary heart disease cannot be made by ECG alone, and combining an imaging test such as exercise myocardial scintigraphy with exercise echocardiography may be useful.[13]

## 1.3 Safety and Points to Check

Exercise ECG is generally safe;[14] however, because it is a stress test, it must be assumed that myocardial ischemia could be induced and may lead to a cardiac event.[15] Accordingly, prior to performing this test it must be explained to the patient that there is a certain risk of myocardial infarction or even sudden death. It is also necessary to obtain a signed consent form. In addition, an emergency cart with a defibrillator, drugs, infusion sets, and intubation tubes should be available in the laboratory in case an emergency occurs, and the quickest route to the emergency department should be identified.

The test should be conducted under the supervision of a highly experienced doctor and several ancillary staff, including laboratory technicians and nurses, with the symptoms, ECG, heart rate, and blood pressure being monitored. In addition to assessing electrocardiographic changes at the onset of symptoms, great care should be taken to not overlook asymptomatic ischemic changes, arrhythmias, or changes in blood pressure.

## 1.4 Protocols

Exercise ECG methods include the classical Master two-step test, the treadmill test, and the bicycle ergometer test. The Master test can be single (1.5 min), double (3 min), or triple (4.5 min). Because the Master test is relatively simple and does not require a special device for exercise, it has been widely used in the present time.[14] However, it is preferable to use the treadmill or ergometer method because the exercise load cannot be controlled during the Master test. Accordingly, exercise tolerance cannot be evaluated with the Master test, although it is an important prognostic indicator, and electrocardiographic changes cannot be captured during exercise. Particularly, this test should not be performed in high-risk patients.

As for the treadmill test, the Bruce protocol is a widely used standard for increasing the speed and inclination of the treadmill (**Table 6**).[16] The duration of the light exercise

| Table 8. Criteria for Ischemia on Exercise Stress ECG |
|---|
| **Definite criteria** |
| ST depression |
| >0.1 mV horizontal, downsloping |
| (measure 0.06–0.08 s after J point) |
| ST elevation |
| >0.1 mV |
| ST depression at rest |
| >0.2 mV horizontal, downsloping |
| **Reference finding** |
| Appearance of negative U wave in the precordial leads |
| **Findings suggesting false positive** |
| HR-ST loop rotates counterclockwise |
| When upsloping ST depression during exercise gradually changes to horizontal or downsloping after exercise and continues for a long time (late recovery pattern) |
| ST changes associated with left ventricular hypertrophy |
| Early recovery from ST change |

(Reproduced from Yamashina A et al 2009,[2] with permission.)

| Table 9. Recommendations and Levels of Evidence for Exercise ECG | | | | |
|---|---|---|---|---|
| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
| Diagnostic purpose of chronic coronary heart diseases | I | B | C1 | IVb |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

stage may be shortened in subjects with a high exercise capacity, based on the interview conducted before examination. On the other hand, the initial load may be increased more slowly in subjects with a low exercise capacity, patients with a low angina pain threshold, and elderly persons. In principle, the symptom-limited load should be applied with reference to the criteria for stopping exercise (**Table 7**),[17,18] and the Borg scale[19] is a useful index for symptoms. A Mason-12-lead unit is used for ECG, in which electrodes attached to the shoulders and near the ilium bilaterally are substituted for the limb leads, and ECG and blood pressure are continuously monitored during the examination.[20] If the target heart rate (85–90% of the expected maximum heart rate [i.e., 220–age/min]) is not reached, the result is judged to be indeterminable because of insufficient exercise loading (even if no ischemic changes are observed).

The major difference between the ergometer and treadmill methods is that the load can be increased in a non-stepwise fashion with the bicycle ergometer. However, the increase in the exercise load per minute is usually set in a range of about 10–20 W so that the maximum load is reached after about 8–12 min.[21] A disadvantage of using an ergometer is that exercise may be terminated because of quadriceps fatigue before the target heart rate is reached in subjects who are not familiar with this method. When an exercise test is performed, exercise should be discontinued if the subject wishes to stop or develops symptoms/signs, such as mild chest pain with ST depression, or moderate chest pain, dyspnea, leg fatigue, or general fatigue without ST depression.

## 1.5 Indices for Evaluation

### 1.5.1 ST Depression

In the double Master test, ST depression of 0.1 mV has been reported to show a sensitivity of 77% and specificity of 83% for detecting ≥75% coronary artery stenosis.[22] In Japan, horizontal or sagging ST depression of ≥0.1 mV is the most common criterion for a positive test.[14] When the treadmill test is performed, the most common criterion for myocardial ischemia is the extent of ST-segment depression from baseline (PQ junction) at 0.06–0.08 s after the J point (**Table 8**).[2] The test is judged to be positive when depression of ≥0.1 mV occurs and the ST segment is horizontal or sagging.[21] If ST depression is present on resting ECG, a further decrease of 0.2 mV from the resting level is the criterion for a positive result.[6,23] An upsloping ST segment that shows depression during exercise, gradually changes to horizontal or sagging after the finish of exercise, and then persists for a long time with T-wave inversion suggests a false-positive result.[24]

In patients with coronary heart disease, it is known that ST depression occurs more frequently as more coronary branches are affected by stenosis.[25] ST depression of ≥0.2 mV, ST depression that occurs with light exercise, a poor blood pressure response to exercise, and low exercise tolerance are indicators of an adverse prognosis.[26–31] Even if ST depression is significant, a small ST/HR slope raises the possibility of a false-positive result.[32] In addition, if the ST/HR slope shows counterclockwise rotation, the probability of a false-positive result is high.[33]

ST elevation is assessed by measurement from the pre-exercise ST level. ST elevation in leads except V1 suggests transmural ischemia. In patients with a history of myocardial infarction, ST elevation with an abnormal Q wave may be caused by abnormal wall motion or reciprocal changes due to ischemia in other regions in addition to ischemia of the infarcted myocardium.[34–36]

### 1.5.2 Other Findings

A negative U wave in the anterior precordial leads suggests myocardial ischemia.[37] Because the baseline shifts during exercise, it is difficult to correctly evaluate; it is necessary to observe the baseline with the patient in a stable condition immediately after the end of exercise. Detection of a negative U wave is not sensitive, but shows high specificity, and has been reported to indicate central involvement of the left anterior descending artery,[38] and to be an indicator of a poor prognosis. It has also been reported that a positive U wave in the right chest leads during exercise reflects posteroinferior wall ischemia and suggests a lesion in the left circumflex artery or the right coronary artery. Although it has been reported that the R wave height and the Q wave depth are useful for diagnosis of coronary heart disease, the specificity of such findings is considered not to be high.[39–42]

In patients with bundle branch block,[43,44] WPW syndrome,[6] or using digitalis,[45] ST depression is not a criterion for diagnosis of coronary heart disease.

## 1.6 Future Challenges

Exercise ECG is the most common test performed for patients with chest pain, but the chief problem is that its sensitivity and specificity are not necessarily high. According to a meta-analysis of 24,074 subjects, diagnosis of coronary heart disease based on ST depression of 0.1 mV showed a

sensitivity of 68% and specificity of 77%.[21] Similarly, Japanese reports covering 1,055 subjects indicated that the sensitivity and specificity of this criterion were 73% and 74%, respectively.[25,46–48] Additional information should be obtained in high-risk patients with negative exercise ECG, low-risk patients with positive exercise ECG, and patients who show abnormal Q waves or ST changes on resting ECG (**Table 9**).

## 2. Holter Electrocardiography

### 2.1 Characteristics and Technical Aspects

Holter ECG is a method of ambulatory monitoring that is characterized by recording for an extended period (24–48 hours), while allowing the subject the freedom to participate in normal daily life. However, it may be difficult to respond to the occurrence of a hazardous electrocardiographic change because analysis is performed after recording has been completed. Moreover, Holter ECG often provides a limited amount of information because of the small number of leads (usually 2–3), although 12-lead Holter ECG has become available in recent years.

In addition to typical Holter ECG, other ambulatory ECG examinations include wireless 1- or 2-lead Holter ECG, extracorporeal or implantable event-switched loop recording, and portable ECG. These methods have value in the diagnosis of arrhythmias and syncopal attacks.

The disposable electrode that is used remains electrically and mechanically stable for a long time. The recorder is compact and lightweight for portability, is robust, and remains electrically and mechanically stable for an extended period. A digital card or IC memory recorder is used for recording information. The speed and accuracy of analysis have been improved thanks to recent remarkable developments in computers. However, the accuracy of the time base, the false-positive and false-negative rates of waveform analysis, and the reproducibility of results vary among manufacturers.[49]

### 2.2 Points to Consider

#### 2.2.1 Selection of the Lead System and Recording Time

Appropriate ECG recording is essential for making a diagnosis of coronary heart disease. Care should be exercised with regard to selection of the electrodes, leads, paste, and lead system to obtain stable recordings during daily activities. The leads that are most likely to reflect ischemic changes are V5-like leads. In particular, lead CM5 is less affected by body movements and has a good detection rate for ischemic changes.[50] A 2-lead system is commonly used, and the AHA guidelines recommend a combination of leads that approximates leads V1 and V5.[51] For capturing ST elevation in patients with variant angina, vertical leads (II, III, and aVF) and approximations to lead V2 or V3 provide a high diagnostic rate.[52] Both circadian and diurnal (day-to-day) variations may exist in relation to the incidence and duration of myocardial ischemia and the extent of ST changes. However, it is difficult to evaluate the influence of diurnal variation based on 24-hour recording, which means that 48-hour recording is desirable for detecting myocardial ischemia and determining the response to treatment.

#### 2.2.2 Criteria for ST-Segment Changes

The diagnostic significance of persistent ST depression on Holter ECG is not high. Rather, detection and evaluation of transient ST-segment changes is more important. The criteria for ST depression are as follows: (1) horizontal or sagging depression of the ST segment by ≥0.1 mV; (2) reaching maximum ST depression after 1 min; and (3) ST depression of ≥0.1 mV lasting for ≥30–60 s compared with the baseline in a controlled state.[49,53–55] ST depression is measured at 0.08 s after the S or J point, and J-type ST depression is not judged to be ischemic ST depression.[52] When counting the number of ischemic episodes, the definition adopted is that each ischemic interval should last for at least 1 min.[56] The criterion for ST elevation is elevation of the ST segment by ≥0.1 mV lasting for ≥30–60 s in leads without Q waves.[49] In patients with chest pain and normal resting electrocardiographic findings, research on Holter ECG, treadmill exercise ECG, and coronary angiography has shown that the sensitivity and specificity of Holter ECG for diagnosis of coronary lesions is 62% and 61%, respectively, being lower than the sensitivity and specificity of treadmill exercise ECG (67% and 75%, respectively).[57]

#### 2.2.3 Factors Influencing Assessment of ST-Segment Changes

When evaluating ischemic ST changes on Holter ECG, it is important to discriminate nonischemic ST changes associated with postural changes.[52,54,55] ECG should be recorded in advance in the supine, lateral, or standing position, or during hyperventilation, and then used as a reference.[49] Ischemic ST-segment changes occur gradually with an increasing heart rate and it often requires 1 min or longer for the maximum change to develop. The ST-segment trend shows a wedge-shaped change when the cause is ischemia. On the other hand, postural ST changes occur rapidly (in several beats to several seconds) together with baseline fluctuation due to the change of posture, and the ST segment trend shows a box-shaped change.[52]

A variety of factors can influence assessment of ST depression.[58] Digitalis can give rise to ST depression with a "sagging" morphology. Some antiarrhythmic drugs, antidepressants, and sedatives cause ST-T changes caused by alterations in repolarization. Hypokalemia and hyperpnea may also induce ST changes. ST-T changes caused by repolarization abnormalities associated with left ventricular hypertrophy, intraventricular conduction defects, or preexcitation syndromes (WPW syndrome, etc.) can be difficult to distinguish from ST-segment changes associated with myocardial ischemia. However, evaluation of ST-segment changes in the left chest's lead is possible in patients with right bundle branch block. Nonspecific ST depression in patients with atrial fibrillation, atrial flutter, and tachyarrhythmias can also lead to false-positive results. In women, horizontal ST depression is often noted even if there are no coronary artery lesions. Thus, the diagnostic accuracy of Holter ECG for myocardial ischemia is low when nonspecific electrocardiographic changes occur because of factors influencing the assessment of ST depression, and in such cases cardiac radionuclide imaging and CCTA are recommended instead.

### 2.3 Significance in the Diagnosis of Chronic Coronary Heart Disease

In patients with chronic coronary heart disease, the suitable conditions for Holter ECG include vasospastic angina, effort angina with significant coronary artery stenosis, and

**Table 10. Recommendations and Levels of Evidence for Indications for Holter ECG for Ischemia Monitoring for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Patients with strongly suspected variant angina, who show unexplained syncope and palpitation | I | C | B | IVb |
| Patients with suspected variant angina | IIa | C | B | IVb |
| Preoperative evaluation for vascular surgery of patients who cannot exercise | IIa | C | B | IVa |
| Evaluation of patients with chest pain who cannot exercise | IIa | C | C1 | VI |
| Asymptomatic patients aged over 20 years with type 2 diabetes mellitus or impaired glucose tolerance who have no history of organic heart disease but who do have ≥1 coronary risk factors | IIb | C | B | IVa |
| Patients with known coronary artery disease and atypical chest pain syndrome | IIb | C | C1 | VI |
| Initial evaluation of patients with chest pain who are able to exercise | III | C | C2 | VI |
| Routine screening of asymptomatic subjects | III | C | C2 | VI |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence. (Reproduced from Crawford et al 1999,[50] Japanese Circulation Society, 2013,[63] and Nakao et al 2015,[70] with permission.)

asymptomatic myocardial ischemia.[49,52,59,60] Holter ECG is more useful than exercise ECG because it can be used to assess myocardial ischemia during daily activities and for preoperative risk assessment in patients who cannot perform exercise because of physical disability, peripheral vascular disease, or severe pulmonary disease.[50] In addition, 12-lead Holter ECG may be performed to improve the diagnosis of myocardial ischemia, especially asymptomatic myocardial ischemia or transient ischemic events.[61]

Analysis of ST-T changes on the 12-lead recording may allow localization of the sites of myocardial ischemia, even silent or transient ones, and has been reported to be more useful than conventional 2-lead Holter ECG, particularly for detecting ischemia of the posteroinferior wall.[62] 12-lead Holter ECG is also useful for detecting arrhythmias and identifying the site of origin, as well as for confirming the pacing status after cardiac resynchronization therapy in patients with heart failure.[61] The guidelines proposed by the Japanese Circulation Society and the AHA regarding the indications for Holter ECG in patients with coronary heart disease and vasospastic angina are summarized in **Table 10**.[50,63,70]

### 2.3.1 Asymptomatic Coronary Heart Disease

Asymptomatic myocardial ischemia is defined as objective evidence of myocardial ischemia in patients without symptoms of ischemia.[64] It is common in the elderly,[65,66] and in patients with diabetes.[67–70] A diagnosis of asymptomatic myocardial ischemia is made by integrating the findings of Holter ECG, exercise testing, and stress myocardial scintigraphy.[52]

Cohn classified asymptomatic myocardial ischemia into 3 types (**Table 11**).[71] The prevalence of transient myocardial ischemia in apparently healthy adults, corresponding to Cohn's type I, has been reported to be 1.2–6% in Western countries based on the results of exercise testing.[72,73] On the other hand, the false-positive rate for ischemic ST depression on Holter ECG is 2–30% (mean: 10.3%) in healthy individuals,[66,74] and it is extremely difficult to identify transient asymptomatic ischemic ST changes in apparently healthy individuals by this method. In individuals with Cohn's type II or III asymptomatic ischemia, the detection rate by Holter ECG is 22–59% (mean: 35%) in Western countries.[75] Similar results have also been reported in Japan,[76,77] with Holter ECG being more useful in these groups compared with patients with Cohn's type I asymptomatic ischemia. When angina pectoris is stratified by the pattern of angina attacks, a closer relationship with coronary tonus is associated with a higher frequency of angina pectoris.[49]

**Table 11. Classification of Silent Myocardial Ischemia**

| | |
|---|---|
| Type I | Totally asymptomatic |
| Type II | Myocardial infarction but now totally asymptomatic |
| Type III | Angina present, but for each anginal episode ≥1 painless episodes can also be documented |

(Reproduced from Cohn 1985,[71] with permission.)

It has been reported that asymptomatic myocardial ischemia is associated with cardiovascular events in patients with diabetes mellitus. When Holter ECG was performed in patients with type 2 diabetes mellitus or impaired glucose tolerance who had no cardiac symptoms despite a 20-year or longer history of diabetes mellitus and risk factors for arteriosclerosis, those showing moderate to severe ischemic ST-T changes and arrhythmias had a high rate of coronary heart disease, and they also had a significantly higher cumulative incidence of future cardiovascular events.[70] On the other hand, it has been reported that routine screening for myocardial ischemia is not recommended in asymptomatic patients with type 2 diabetes mellitus and normal electrocardiographic findings.[78] No conclusion has yet been reached regarding the balance between the benefits, costs, and risks of testing for myocardial ischemia in asymptomatic patients.[79]

#### 2.3.2 Effort Angina

Holter ECG can be used to detect ischemic changes and to examine the frequency of transient ST-segment changes in daily life, as well as the timing of onset, severity of ST depression, relationship with the heart rate, and circumstances in which ischemic changes occur.[80] It is also useful for identifying arrhythmias associated with episodes of myocardial ischemia. In patients with stable angina, Holter ECG has a 20–45% probability of detecting myocardial ischemia, and the presence of myocardial ischemia is reported to be associated with future coronary events.[50] However, the limitations of Holter ECG make it difficult to assess the site or severity of ischemia.[49] In patients in whom the extent of stenosis is clarified by coronary angiography, etc., it is useful for investigating the relationship between daily activities and transient myocardial ischemia or for pharmacological evaluation of antianginal drugs.[81]

#### 2.3.3 Vasospastic Angina

This disease is essentially unstable angina, corresponding to Class II (subacute rest angina) or Class III (acute rest angina) in the classification,[82] and must therefore be evaluated promptly. In many cases, the diagnosis can be made by taking a detailed history of the event, and Holter ECG is useful for confirming the diagnosis based on the electrocardiographic findings at the time of symptoms.[49] Among patients with vasospastic angina, only about 20–30% exhibit ST changes associated with chest pain, and asymptomatic coronary artery spasm is common.[63] During an attack, electrical alternans or lethal arrhythmias such as ventricular tachycardia and ventricular fibrillation may occur. When this disease is suspected based on symptoms or the history, it is desirable to record a V5-like lead in combination with any of the II, III, or aVF-like leads representing the electrical activity of the lower axis of the heart, which tends to reflect electrocardiographic changes caused by spasm of the right coronary artery.[52] If possible, multichannel or 12-lead Holter ECG should be recorded rather than a 2-channel electrocardiogram. In addition, recording for 48 hours rather than 24 hours is more likely to identify an attack.[63]

Holter ECG is also used to evaluate the response to treatment after diagnosis. In patients with this vasospastic angina, transient myocardial ischemia usually occurs from around midnight to the early morning. Hence, Holter ECG is the best option for detecting these electrocardiographic changes, and vasospastic angina seems to be the most suitable indication for use of Holter ECG. In the active phase, it is often necessary to record Holter ECG twice or more per month after hospitalization in order to evaluate the effect of antianginal drugs. However, it should be noted that Holter ECG is currently permitted only once a month in Japan as a healthcare service covered by health insurance.[49]

### 2.4 Future Challenges

Currently, continuous recording of Holter ECG for an extended period is the most widely used method of ambulatory ECG, and a digital card or built-in memory is used for recording data. These devices allow automatic and continuous recording for a long time. In addition to the role of Holter ECG in evaluation of transient ST changes associated with coronary heart disease, it is useful for determining the time period during which acute myocardial infarction, angina pectoris, and cardiac death occur from the perspective of chronobiology,[83] and in assessment of autonomic nervous system activity and for estimation of the prognosis by analysis of heart rate variability.[84–86] It is expected that the accuracy of diagnosing coronary heart disease can be improved by use of 12-lead Holter ECG recording systems.

An event-triggered device, which is designed to be carried for several days to detect infrequent events, has also been developed, as well as a transmitting device capable of transmitting the electrocardiogram in case of emergencies. In the future, it will be important to use the most appropriate portable electrocardiographic device according to the pattern of cardiac events and the objectives. It is also important to consider the aspect of medical cost efficiency.

## 3. Signal-Averaged Electrocardiography, T-Wave Alternans, Body Surface Potential Mapping, and Magnetocardiography

SAE is a method of detecting the ventricular late potentials (LPs), which are the delayed potentials at the end of the QRS complex, by summing and averaging tiny electrocardiographic signals that cannot be recorded with conventional surface ECG.[87] The ventricular LPs reflect "depolarization (conduction) abnormality" because they are part of the QRS complex, and the LPs are therefore used as a predictor of lethal arrhythmias or sudden cardiac death.[88,89] It is a simple test and widely used in Japanese hospitals specializing in cardiology.

### 3.1 Signal-Averaged Electrocardiography

#### 3.1.1 Characteristics and Technical Aspects

SAE involves recording tiny potentials from the body surface that can otherwise only be recorded from the cardiac chambers. This is made possible by averaging multiple electrocardiographic waveforms together with processing to reduce noise. When ventricular LPs are recorded (**Table 12**), it is judged that a sustained ventricular arrhythmia is likely to occur. SAE was approved as a method for predicting lethal arrhythmia that is covered by insurance in the 2012 revision of remuneration for medical services.

To detect ventricular LPs by SAE, the X, Y, and Z leads are first recorded for at least 90–150 beats and then are summed and averaged. Next, the summed and averaged electrocardiogram is filtered and 3-lead electrocardiograms are synthesized to produce a spatial (vector) magnitude electrocardiogram. Thus, it is possible to detect the small LPs at the end of the QRS complex. In recent years, it has become possible to perform SAE analysis by averaging the Holter ECG waveforms. The standard for a positive test differs among manufacturers of SAE units. It should be noted that patients with bundle branch block are excluded. The presence of right or left bundle branch block inevitably prolongs the QRS complex, often with extension of $LAS_{40}$ as well, and this causes a positive result.

#### 3.1.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

The mechanism underlying sustained arrhythmia is reentry. Reentrant arrhythmias (especially sustained ventricular tachycardia) sometimes occur after myocardial infarction, and can be fatal. Existence of unidirectional block and conduction delay are both required for reentry to be

**Table 12. Parameters for Measuring Ventricular LP and Its Determination for Positivity**

| Parameter | Definition | Meaning | Determination |
|---|---|---|---|
| fQRS (ms) | Filtered QRS duration | Total time for ventricular depolarization | >135 ms |
| $RMS_{40}$ ($\mu$V) | Root mean square voltage of the potential at the terminal 40 ms of the QRS complex | Level of low potential at the end of ventricular depolarization | <15 $\mu$V |
| $LAS_{40}$ (ms) | Duration of a low amplitude potential <40 $\mu$V at the end of the QRS complex | Duration of low potential at the end of ventricular depolarization | >39 ms |

When ≥2 of the 3 criteria (fQRS >135 ms, $RMS_{40}$ <15 $\mu$V, and $LAS_{40}$ >39 ms) are met, ventricular LP is determined as positive.

**Table 13. Parameters for Measuring M-TWA With Exercise Loading and Its Determination for Positivity**

| Parameter | Definition | Meaning | Determination |
|---|---|---|---|
| Alternans voltage ($\mu$V) | Alternating potential: a parameter reflecting the extent of TWA | Degree of alternating potential in ventricular repolarization | >1.9 $\mu$V |
| Alternans ratio | Parameter representing the reliability of data as the ratio of the alternating potential to background noise | Reliability of alternating potential in ventricular repolarization | >3.0 |

When both criteria (alternans voltage >1.9 $\mu$V and alternans ratio >3.0) are met, M-TWA is determined as positive.

established. Unidirectional block cannot be identified before the arrhythmia is established. In contrast, conduction delay can be confirmed by the presence or absence of ventricular LPs. Thus, the LPs were used to predict the risk of hazardous, sustained ventricular tachycardia and sudden cardiac death. When stratified by the underlying heart disease, the predictive value of ventricular LPs has been best established after myocardial infarction.[90–94] However, clinical research has been published that did not confirm the usefulness of the LPs for predicting sudden cardiac death (mainly that caused by ventricular fibrillation) in patients with CAD,[95] so their reliability is not rated as highly as in the past.

### 3.1.3 Future Challenges

Ventricular LPs were frequently used to predict sustained ventricular tachycardia after myocardial infarction until about the year 2000. In recent years, however, it has become clear that there are more useful predictors. Hence, LPs are less commonly investigated alone, and more often combined with other noninvasive predictors.[94]

## 3.2 T-Wave Alternans

TWA is beat-to-beat variation in the polarity or amplitude of the T-wave (ABABAB...). It can be detected noninvasively at the microvolt level.[96] TWA reflects abnormal ventricular repolarization and is used as a predictor of lethal arrhythmias or sudden cardiac death. Albeit it is a simple test, it is mainly performed at hospitals specializing in arrhythmia because it requires exercise testing and the electrodes are relatively expensive.

### 3.2.1 Characteristics and Technical Aspects

TWA is often observed just before the onset of ventricular fibrillation. The measurement of TWA is based on the hypothesis that patients at risk of ventricular fibrillation should have low-level TWA even in the stable phase. Much evidence has been published about microvolt TWA (M-TWA) measured by spectral analysis of electrocardiograms recorded during exercise.[88,89] Measurement of M-TWA (**Table 13**), which requires an exercise test, was approved for prediction of lethal arrhythmia as an item covered by health insurance in the 2012 revision of remuneration for medical services.

Because there is a heart rate threshold for the appearance of TWA, it is necessary to increase the heart rate to a certain level (≈110–120 beats/min) by exercise with an ergometer or treadmill at the time of measurement. Pacing may be used, but this is only possible with atrial pacing. The criteria for M-TWA positivity are an alternans voltage (alternating potential: a parameter reflecting the extent of TWA) of ≥1.9, and an alternans ratio (a parameter representing the reliability of data as the ratio of the alternating potential to background noise) >3.0 in leads X, Y, Z or the adjacent chest leads that occur at a heart rate ≤110 beats/min and persist for ≥1 min. If these criteria are not satisfied, the result is negative. If a definite judgment cannot be made, the result is classified as undeterminable.

In patients with persistent atrial fibrillation or frequent extrasystoles, it is difficult to detect alternans and therefore analysis is impossible. Because there is a heart rate threshold for the appearance of TWA, the measurement needs to be performed after the heart rate has been increased by performing exercise. However, the heart rate cannot be increased to the desired level in patients who have severe bradycardia or are on $\beta$-blockers, leading to "undeterminable" results.

### 3.2.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

There is considerable evidence about the usefulness of M-TWA in patients with heart diseases such as myocardial infarction and ischemic cardiomyopathy.[97–100] It has been shown to be useful for predicting sudden cardiac death in patients with myocardial infarction, regardless of their cardiac function.[97] Large clinical trials have been performed that only enrolled patients with poor cardiac function,[101,102] and these showed that M-TWA is more useful for predicting

all-cause death or cardiac death than for predicting lethal ventricular arrhythmias. There have been recent reports about the usefulness of detecting TWA by Holter ECG in patients with myocardial infarction and ischemic cardiomyopathy.

#### 3.2.3 Future Challenges

Two new methods of detecting TWA have recently become available and are already in clinical use.[103] One is a simple method of detecting TWA continuously over 24 hours by using time-domain analysis to determine the modified moving average (MMA) of Holter ECG data (MMA-TWA). However, there is insufficient evidence about the usefulness of these methods, and this is a subject for future research.

### 3.3 Body Surface Potential Mapping

The current reference system is the 87-lead method developed by Watanabe et al.[104] It is used to identify the site and severity of myocardial ischemia and infarction, and to evaluate the risk of ventricular arrhythmia.

#### 3.3.1 Characteristics and Technical Aspects

Body surface potential mapping involves collection of electrocardiographic information from the surface of the thorax (precordium and back), which makes it different from vectorcardiography (fixed electrical potential) or standard 12-lead ECG (fewer leads and some bipolar leads). This test is covered by health insurance.

The device manufactured by Fukuda Denshi is currently the standard system used in Japan. Its 87 leads are arranged mainly in the precordial region and a few on the patient's back by surrounding the chest wall using sheets with 13 rows of electrodes (A–M), and potentials are recorded with Wilson's central terminal electrode as the indifferent electrode. Columns A, E, and I are placed on the right midaxillary line, midsternal line, and left midaxillary line, respectively, while columns B, C, and D are placed so that columns A and E are equally divided into 4. Similarly, columns F, G, and H are arranged so that columns E and I are equally divided into 4. Column J is positioned so that the distance between columns I and J is equal to the distance between columns H and I.

In the same manner, column M is positioned so that the distance between columns M and A is equal to the distance between columns A and B. With regard to positioning of the rows, rows 6 and 4 are placed on the midline of the sternum at the level of the second and fifth intercostal spaces, respectively, and then row 5 is placed between rows 6 and 4. Rows 7, 3, 2, and 1 are positioned so that the space between each row is equal. Rows 6 and 7 do not exist in columns A and I located in the axillary regions. Thus, body surface potentials must be recorded using specialized sheet electrodes, the supply of which is gradually shrinking because a new product has not been developed.

#### 3.3.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

Body surface potential mapping can provide detailed information on the location and extent of myocardial infarction and myocardial ischemia. The map is the most frequently used display method, because it allows diagnosis of myocardial infarction that is impossible to diagnose with standard 12-lead ECG.[105,106] Localization of ischemic regions is also improved by recording T-wave and ST-segment electrograms.[107,108] The map contributes to accurate quantitation of the infarcted area.[109,110] In addition, it is possible to estimate the location of regions of ischemic myocardium by creating an ST-T map,[111] which can also be used to assess the risk of severe ventricular arrhythmia.[112] The isochrone map can be used to evaluate ischemic regions after exercise.[113]

#### 3.3.3 Future Challenges

Although body surface potential mapping is covered by health insurance, it is currently only used at a few institutions. The reasons are that recording and analysis are troublesome, and even maintenance is not easy because new models are not being developed. Moreover, other modalities that can directly evaluate cardiac morphology and function, such as echocardiography, cardiac MRI, and cardiac radionuclide imaging, have become more important for diagnosis.

### 3.4 Magnetocardiography

#### 3.4.1 Characteristics and Technical Aspects

Because magnetocardiography directly measures the magnetic fields generated by electric currents in the heart,[114] there is no distortion of information such as occurs with ECG (P wave, QRS complex, and ST segment), and the sensitivity is higher than that of electrocardiograms obtained by measurement of electrical potentials. The location of the current source can be easily estimated by extracting information on the myocardial current just beneath the sensor. As body surface electrodes are not required, it is unnecessary to filter the direct current component of the signal, and deviation can be evaluated as an absolute value relative to the ST segment. Magnetocardiography became covered by health insurance in 2003.

To perform magnetocardiography, a special superconducting magnetic sensor called a superconducting quantum interference device (SQUID) is used to measure tiny magnetic fields generated on the body surface as the heart beats. The information thus obtained can be used to display an image of the heart, as with echocardiography or cardiac radionuclide imaging. Thanks to technical advances, it is also possible to display 3-dimensional images using devices manufactured by Hitachi High-Technologies. Multichannel devices that can cover the entire heart simultaneously are becoming increasingly popular, solving the problems of spatial positioning accuracy and reproducibility between sensors, and noninvasive noncontact measurement can now be performed while the subject is wearing clothing.

#### 3.4.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

Magnetocardiograms can be displayed as a time waveform map, magnetic field (distribution) map, current arrow map, current integral map, current ratio map, etc. The time waveform map displays the magnetic field strength as a waveform similar to an electrocardiogram, and can be used to accurately evaluate ST-segment deviation (an ischemic change).[115] By summing and averaging to detect very weak signals, the substrate of ventricular tachycardia can also be examined.[116] It is also possible to evaluate the existence of regions of infarcted and ischemic myocardium that are difficult to diagnose by body surface ECG.[117]

The current arrow map delineates the current at each

point as a vector arrow based on the magnetic field gradient (spatial difference) between 2 adjacent points, and it is useful for estimating the origin of extrasystoles.[118] In addition, the reentry point of a sustained arrhythmia can be displayed as an arrow. Current integral mapping is useful for obtaining the sum of the currents of the depolarization process (QRS complex) and the repolarization process (JT segment) and can be used to detect ventricular repolarization abnormalities at rest.[119] The current ratio map is used to display changes in the current in the magnetocardiographic QRS complex after mild exercise, and is useful for detecting ischemic changes.[120]

### 3.4.3 Future Challenges

Magnetocardiography is characterized by rapid noninvasive acquisition of data while the subject remains clothed, and provides a large amount of information. However, it is not a widely used test, possibly because no consensus has been established about the methods of measurement and analysis and because the equipment is expensive. Currently, it is only used at a few centers in Japan. Recommendatios and levels of evidence for SAE, TWA, body surface potential mapping and magnetocardiography are shown in **Table 14**.

**Table 14. Recommendations and Levels of Evidence for LP, TWA, Body Surface Potential Mapping, and Magnetocardiography for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| LP | IIb | C | B | IVa |
| TWA | IIb | C | B | IVa |
| Body surface potential mapping | IIb | C | C1 | IVb |
| Magnetocardiography | IIb | C | C1 | IVb |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

## 4. Resting Echocardiography

### 4.1 Significance in the Diagnosis of Chronic Coronary Heart Disease

Resting echocardiography provides information on the treatment and prognosis of patients with chronic coronary heart disease, especially those who have hypertension or valvular disease.[2,49] It is also useful for diagnosis of other comorbidities. The greatest advantages of echocardiography are that it is simple to perform and relatively easy to repeat. It has been reported that detection of cardiac dilatation and dysfunction by resting echocardiography has prognostic significance in patients with chronic coronary heart disease.[121,122] Treatment strategies are determined based on the LVEF and global assessment of cardiac contractility, regional wall motion abnormalities, diastolic function, left ventricular filling, and the presence/absence of pulmonary hypertension.[123,124]

If echocardiography reveals regional wall motion abnormalities in the territory of multiple coronary arteries and thus suggests coronary heart disease with extensive ischemic regions, rapid performance of diagnostic angiography is warranted, such as CCTA, or coronary angiography.[125] The left ventricle is often poorly visualized by echocardiography in obese patients or those with pulmonary disease, prior thoracic surgery, or chest deformity. Use of an ultrasound contrast agent can improve delineation of the endocardium, but this is not covered by health insurance in Japan.[126]

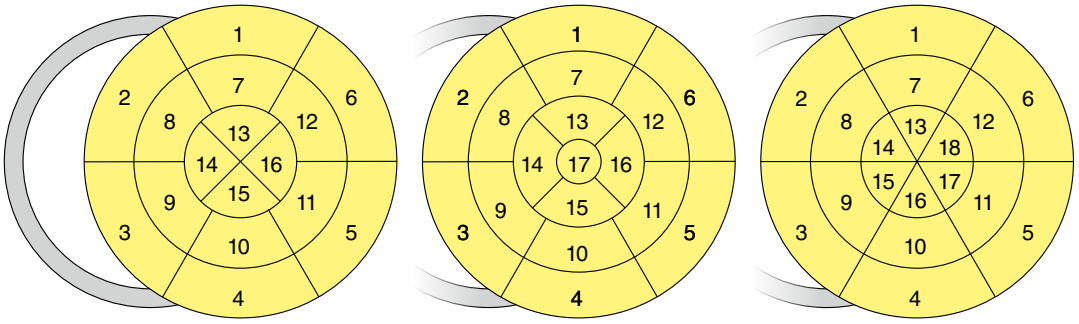
### 4.2 Comparison With Other Tests

Although radionuclide imaging can help to measure LVEF more accurately, it does not provide information on valvular

**Table 15. Recommendations and Levels of Evidence for Resting Echocardiography**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Initial workup by echocardiography is recommended for patients suspected as coronary artery disease to detect regional wall motion abnormality, risk stratification with LVEF measurement, and evaluating LV diastolic function<br>*See **Table 55** | I | B | B | IVa |
| Evaluating LV systolic/diastolic function and myocardial/pericardial abnormalities including Dopplar method are recommended in patients with coronary artery disease presenting abnormal Q waves, heart failure symptoms, complex ventricular arrhythmia or undiagnosed cardiac murmurs<br>*See **Table 55** | I | B | B | IVa |
| Evaluating LVEF and regional wall motion abnormality by echocardiography are recommended for patients with new/worsened heart failure symptoms, or suspected myocardial infarction based on history or ECG during follow-up | I | C | B | IVa |
| Cardiac structural/functional assessment by echocardiography may be recommended for patients with hypertension or diabetes presenting abnormalities on ECG | IIb | C | C1 | IVa |
| Echocardiography is not recommended for routine assessment of cardiac function in patients with normal ECG, no history of myocardial infarction, no symptoms suggesting heart failure, no complex ventricular arrhythmia, and no symptoms suggesting cardiac diseases<br>*See **Table 55** | III | C | C2 | VI |
| Repeated evaluation of cardiac function by echocardiography is not recommended for patients without any changes in clinical status, for whom no change in therapy is planned, and with low risk for cardiovascular events<br>*See **Table 55** | III | C | C2 | VI |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.




**All models**

1. Basal anterior
2. Basal anteroseptal
3. Basal inferoseptal
4. Basal inferior
5. Basal inferolateral
6. Basal anterolateral
7. Mid anterior
8. Mid anteroseptal
9. Mid inferoseptal
10. Mid inferior
11. Mid inferolateral
12. Mid anterolateral

**16 and 17 segment model**

13. Apical anterior
14. Apical septal
15. Aical inferior
16. Apical lateral

**17 segment model only**

17. Apex

**18 segment model only**

13. Apical anterior
14. Apical anteroseptal
15. Apical inferoseptal
16. Apical inferior
17. Apical inferolateral
18. Apical anterolateral

**The following segments may be called in traditional terms (see Table 16):**

3., 9., 15 (18 segment model). : septal; 5., 11., 17 (18 segment model). : posterior; 6., 12., 18 (18 segment model). : lateral

**Figure 1.** Schematic diagram of the left ventricular segmentation models. The anterior septum, inferior septum, inferior wall, inferolateral wall, anterolateral wall, and anterior wall are located counterclockwise from the anterior insertion of the free wall of the right ventricle to the interventricular septum at the base and mid-left ventricle. (Reproduced from Voigt et al 2015[130] and Lang et al 2015,[131] with permission.)

or pericardial disease. Exposure to radiation is another problem. Not all institutions can perform cardiac MRI, but it can assess cardiac function more accurately and provide information on myocardial and valvular structures. Cardiac MRI can also assess the viability of myocardium based on late gadolinium enhancement (LGE), and evaluation of cardiac function and structure is more accurate than with cardiac CT. Although radiation exposure with CT has been reduced markedly over the years, CT and radionuclide imaging are still somewhat problematic to perform in patients with a low probability of disease or younger patients.[126] Echocardiography also has the advantage that it can be easily performed at the bedside.

**Table 16. Left Ventricular Segmental Nomenclature**

| Segment number* | Current terms (ref 131) | Traditional terms (ref 132) |
|---|---|---|
| 1 | Anterior | Anterior |
| 2 | Anteroseptal | Anteroseptal |
| 3 | Inferoseptal | Septal |
| 4 | Inferior | Inferior |
| 5 | Inferolateral | Posterior |
| 6 | Anterolateral | Lateral |

*Same as the number of the basal segments shown in **Figure 1**.

## 4.3 Indications

As described above, much information can be obtained from resting echocardiography and it should be the initial test in patients with suspected coronary heart disease.[127] Because of its simplicity and noninvasiveness, echocardiography is often performed in patients for whom it is not necessary, which places a burden on the staff of institutions and may even lead to lost opportunities to examine other patients who may have benefitted from echocardiography. In recent years, indications for the appropriate use of echocardiography have been proposed.[128] Guidelines for appropriate use of resting echocardiography are not only for primary care but also for specialist centers.[129]

Resting echocardiography is considered appropriate if the patient has symptoms, such as chest pain, or dyspnea, or if the results of radiographic, electrocardiographic, or laboratory tests suggest cardiac disease during initial assessment or follow-up.[126] On the other hand, it is considered inappropriate for routine assessment of cardiac function during follow-up of patients with known coronary heart disease and no changes in their symptoms or clinical findings.[126] Conversely, echocardiographic evaluation is appropriate for acute chest pain or hemodynamic instability.[126] To aid in the appropriate implementation of resting echocardiography while taking the above indications into account and avoiding overuse, specific guidelines for Japan have been proposed based on guidelines from Western countries (**Table 15**).[126–128]

## 4.4 Information Obtained

### 4.4.1 Left Ventricular Systolic Function

The American Society of Echocardiography guidelines suggest that the left ventricle should be divided into 16–18

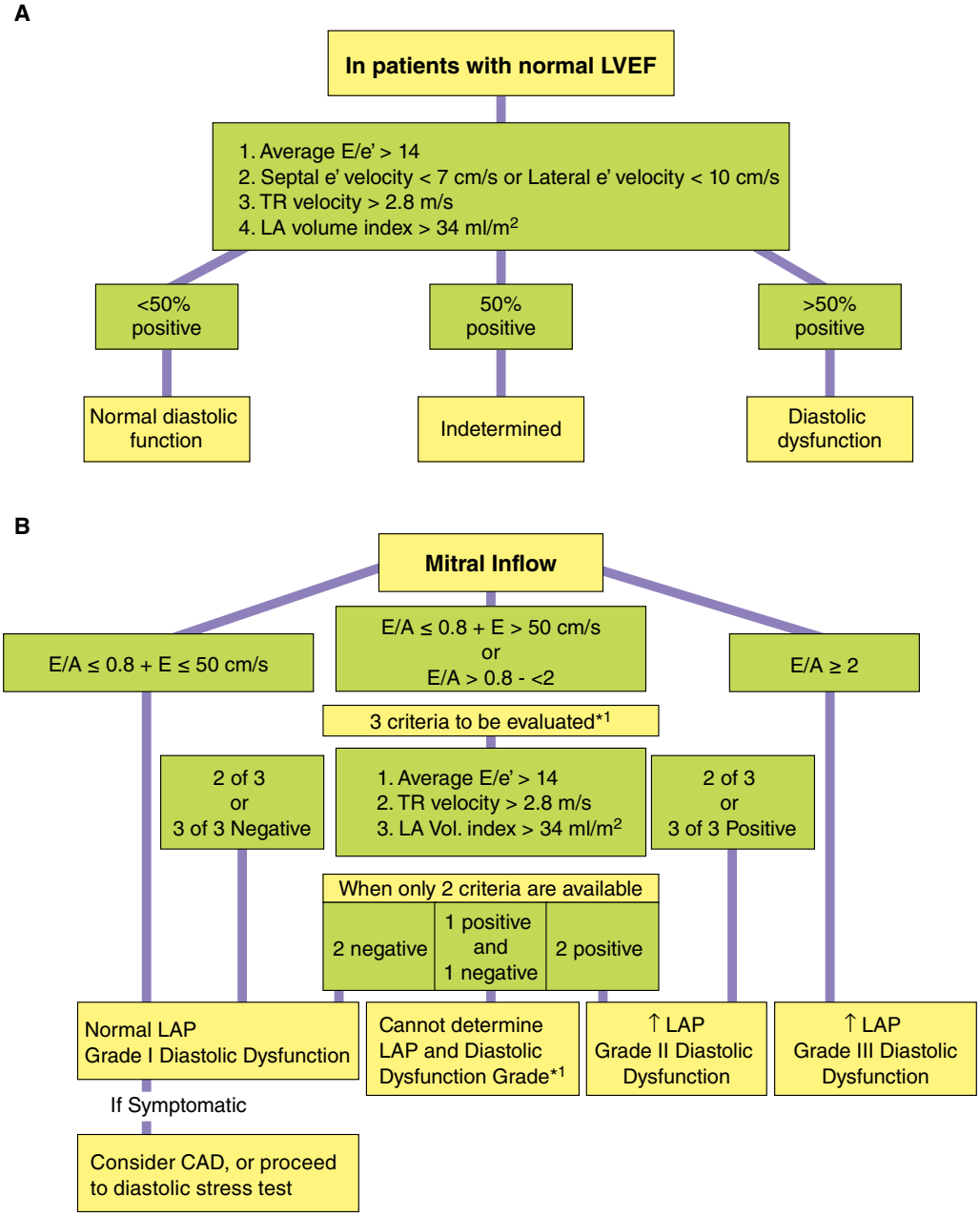



**Figure 2.** Algorithms for evaluating left ventricular (LV) diastolic function and LV filling pressure. (**A**) Algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF. (**B**) Algorithm for estimation of LV filling pressures and grading LV diastolic function in patients with depressed LVEF and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data. CAD, coronary artery disease; LA, left atrial; LAP, left atrial pressure; TR, tricuspid regurgitation. (Reproduced from Nagueh et al 2016[133] with permission from Elsevier. Copyright (2016) by the American Society of Echocardiography.)

segments to assess regional wall motion (**Figure 1**).[130,131] The anterior septum, inferior septum, inferior wall, inferolateral wall, anterolateral wall, and anterior wall are located counterclockwise from the anterior insertion of the free wall of the right ventricle to the interventricular septum at the base and mid-left ventricle. The inferior septum has traditionally been called the septum, and the inferolateral wall and the anterolateral wall were termed the posterior wall and lateral wall, respectively.[132] Because these old terms are still used in many situations in Japan, a table comparing the new and old terms has been provided (**Table 16**). If the cardiac apex is divided into 6 segments in the same way as the basal region and the mid-left ventricle, this results in a total of 18 segments. If the apex is only divided into 4

segments (septum, inferior wall, lateral wall, and anterior wall), there are 16 segments in total, while adding an apical cap segment results in 17 segments.

Wall motion is generally assessed on a 4-point scale: (1) normokinesis or hyperkinesis; (2) hypokinesis (reduced wall thickening); (3) akinesis (no/negligible increase in wall thickness, e.g., myocardial scarring); and (4) dyskinesis (reduced systolic wall thickening and distension). When wall motion is evaluated, each segment should be assessed in multiple sections. In general, 2-dimensional echocardiography is recommended for measurement of left ventricular volume and LVEF by the modified Simpson's method in the 4- and 2-chamber views.

#### 4.4.2 Left Ventricular Diastolic Function

It is known that cardiac diastolic function is a prognostic indicator that is independent of left ventricular systolic function. For evaluation of diastolic function, it is recommended to measure mitral flow parameters, such as the E wave, E wave deceleration time (E-Dct), A wave, and e' wave (by tissue Doppler imaging; mean of the septal and lateral wall values), as well as determining the E/e' ratio, the left atrial volume corrected by body surface area, and tricuspid regurgitation (**Figure 2**).[133]

#### 4.4.3 Direct Visualization of Coronary Flow (Doppler Echocardiography)

Coronary blood flow can be recorded by transthoracic Doppler, especially the blood flow velocity waveform in the distal left anterior descending artery.[134] It is a minimally invasive and useful test, but this technique is not necessarily available at all centers.

#### 4.4.4 Myocardial Viability

Tests that are useful for diagnosing myocardial viability include stress echocardiography, cardiac MRI, SPECT, and FDG-PET. In addition, myocardial thinning and increased brightness on resting echocardiography also suggest poor viability.

#### 4.4.5 Mitral Regurgitation

When cardiac dysfunction occurs and results in left ventricular dilation, it causes mitral tethering that leads to functional and ischemic mitral regurgitation. Regurgitation is judged to be functional/ischemic if the systolic closing position of the leaflet is displaced towards the apex (so-called tenting). Even mild functional and ischemic mitral regurgitation may worsen the prognosis.[135] Mitral regurgitation associated with exacerbation of heart failure is known to be improved by treatment, and it should be re-evaluated after the patient has been stabilized.[136]

#### 4.4.6 Left Ventricular Mural Thrombus

Left ventricular mural thrombus is also detected by echocardiography. It commonly occurs in regions with decreased wall motion. If mural thrombus is suspected, it is also necessary to obtain images that differ from typical cross-sections.

### 4.5 Future Challenges

It has been reported that evaluation of myocardial perfusion by echocardiography using contrast medium provides equivalent results to those obtained with radionuclide imaging. However, this method is not widely used in Japan because of current restrictions on its use.[137]

## 5. Stress Echocardiography

The increase in function that occurs in response to a load is the functional reserve, and tests that involve applying a load to examine this reserve are known as stress tests. In patients with coronary heart disease, the peripheral CFR is reduced beyond the site of stenosis, and wall motion abnormalities are induced by ischemia when stress is imposed. In the context of diagnosis and treatment of chronic coronary heart disease, stress tests are often carried out to detect coronary artery stenosis and evaluate the cardiac reserve. When echocardiography is used for such evaluation, it is called stress echocardiography, and this method is characterized by the ability to not only evaluate regional wall motion abnormalities but also changes in overall cardiac function.

### 5.1 Characteristics and Technical Aspects

Stress echocardiography allows repeated noninvasive evaluation of changes in cardiac hemodynamics, mainly by using tomographic and Doppler methods. The heart rate and respiratory rate increase during exercise, and images are unstable, making evaluation of wall motion more difficult than at rest. In order to overcome these limitations, a quantitative assessment of wall motion is performed using automatic tracing of the endocardial surface, and a method that involves comparison of wall motion in each loading phase by viewing multiple digital images on a screen has also been introduced. Because the reliability of quantitative assessment remains problematic, visual evaluation of wall motion by an examiner viewing multiple digital images is often adopted for evaluation. Visualization of the endocardial surface has been greatly improved in recent years with advances in ultrasonic diagnostic equipment.

Tissue Doppler imaging is also used for evaluation of wall motion abnormalities during stress echocardiography.[138] However, tissue Doppler imaging cannot exclude potential effects caused by movement of the entire heart or traction by adjacent healthy myocardium, and has limitations, such as the velocity recorded being dependent on the angle between the ultrasound beam and the moving direction of the region of interest. To overcome such disadvantages of the tissue Doppler method, strain imaging by 2- and 3-dimensional speckle-tracking echocardiography have been introduced for detection of ischemic regions and evaluation of myocardial viability.[139,140] The loading methods for stress echocardiography in patients with chronic coronary heart disease are shown in **Table 17**.[141–144] Dynamic

**Table 17. Methods of Stress Echocardiography (Including Unlisted for Insurance)**

| |
|---|
| **1. Exercise stress** |
| 1) Dynamic stress (ergometer, treadmill, etc.) |
| 2) Isotonic stress (handgrip, etc.) |
| **2. Pacing stress** |
| **3. Pharmacological stress** |
| 1) Sympathetic agonist (dobutamine, isoproterenol, etc.) |
| 2) Coronary vasodilator (dipyridamole, ATP, etc.) |

methods are more physiological, but recording during exercise is difficult if a treadmill is used. Therefore, it is necessary to obtain images in a relatively short time immediately after the completion of exercise, but it is often difficult to get good images due to the increased respiratory rate. On the other hand, image acquisition is possible during exercise if the patient uses a bicycle ergometer in the supine or semi-sitting position, and it is also possible to assess the level of loading at which wall motion abnormalities appear. Pharmacological stress loading has the advantage that recording images at each stage is relatively easy because the position of the subject is constant. Dobutamine is the preferred stress agent because it is useful for both detection of ischemia and assessment of myocardial viability.

## 5.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

### 5.2.1 Purpose

In patients with chronic coronary heart disease, the primary purpose of stress echocardiography is to detect and assess the severity of significant coronary artery stenosis inducing ischemia. It is also used to predict the prognosis and to assess myocardial viability after recanalization (reperfusion) therapy.[145] That is, stress echocardiography is also used to determine whether resting cardiac dysfunction can be improved by PCI.[146,147]

### 5.2.2 Advantages and Disadvantages

In patients with chronic coronary heart disease, stress testing is used to induce myocardial ischemia and investigate its severity and extent. Exercise ECG is often used for such assessment. However, in patients with ST-T wave abnormalities, bundle branch block, or left ventricular hypertrophy at rest, the adequacy of ECG for assessment of ischemia is doubtful. Stress echocardiography is more sensitive and specific for diagnosing myocardial ischemia than stress ECG because echocardiography allows direct visualization of the presence, severity, and distribution of ischemic wall motion abnormalities.

Compared with stress radionuclide imaging, stress echocardiography is simpler and cheaper to perform because it does not require expensive equipment or difficult-to-handle radiopharmaceuticals. The disadvantages of stress echocardiography are that recording good images is difficult in a certain percentage of patients, and that results are highly dependent on the echocardiographer's skill. These factors are probably the main reasons for the large variation in the sensitivity and specificity of this method among different centers.

### 5.2.3 Results and Their Significance

#### a. Diagnosis of Coronary Artery Stenosis

The site of myocardial ischemia can be evaluated by assessing wall motion abnormalities (and their distribution) that are triggered by loading. Detection sensitivity is higher in patients with multivessel disease than in those with single-vessel disease, and it is also higher in patients with ≥70% stenosis than in those with <70% stenosis.[148,149] Moreover, detection sensitivity is higher in patients with resting regional wall motion abnormalities.[150] The presence, distribution, and extent of myocardial ischemia revealed by stress echocardiography provide useful information for determining the indications for cardiac catheterization. A negative test is associated with a low risk of future cardiac events. Assessment of microvascular function by measuring the CFVR using transthoracic Doppler echocardiography has been introduced.[151] The problems with this method are that measurement of CFVR for the 3 major coronary arteries is impossible in some patients, and that it is not possible to evaluate lesions distal to the site of imaging.

#### b. Evaluation of Myocardial Stunning

If myocardium in the ischemic region is viable, revascularization can improve left ventricular wall motion, and this includes both stunned and hibernating myocardium. Stunned myocardium is viable, but shows long-term functional abnormalities after alleviation of acute ischemia, whereas hibernating myocardium displays chronic depression of contraction due to reduced coronary blood flow. The function of hibernating myocardium can be improved by increasing the myocardial oxygen supply relative to demand, but the clinical problem associated with myocardial stunning is persistent cardiac dysfunction after early reperfusion therapy for acute myocardial infarction.[152] Accordingly, assessment of myocardial viability is critical for predicting the prognosis and selecting treatment modalities.

Against this background, clinical evaluation of stunned myocardium by low-dose dobutamine stress echocardiography has been reported.[153] It is also possible to detect residual myocardial ischemia by simultaneous high-dose dobutamine challenge.[154] Dobutamine stress echocardiography can evaluate both myocardial viability and myocardial ischemia in a single examination, and it is useful for selecting patients with viable myocardium and potential myocardial ischemia and in determining the indications for revascularization. It has been reported that strain imaging is superior for assessing regional wall motion in comparison with visual evaluation of wall motion and tissue Doppler imaging, and thus can more sensitively evaluate myocardial viability.[155]

#### c. Evaluation of Hibernating Myocardium

Clinically, hibernating myocardium can make it difficult to determine the indications for coronary revascularization when left ventricular dysfunction is associated with severe coronary artery stenosis. PET and thallium (Tl)-201 myocardial perfusion imaging have been used for the diagnosis of hibernating myocardium.[156] These methods determine myocardial viability based on myocardial perfusion and metabolic activity. Animal studies have shown that dobutamine challenge can identify the contractility of hibernating myocardium, as in the case of stunned myocardium,[157] and low-dose dobutamine stress echocardiography is used clinically to detect hibernating myocardium.[158] However, it should be noted that there is a theoretical inconsistency in attempting to assess the contractility of failing myocardium with chronic hypoperfusion by administration of a positive inotropic agent that can aggravate myocardial ischemia during prolonged hypoperfusion. In other words, dobutamine challenge may exacerbate myocardial ischemia and thus reduce wall motion (with the contractile response being hidden) despite the presence of viable myocardium.

#### d. Prediction of the Prognosis

Determining the presence/absence of myocardial ischemia during exercise or pharmacological stress echocardiography

is useful for prediction of the prognosis. A negative result of stress echocardiography is associated with a low incidence of future cardiac events.[159] Stress echocardiography is more specific for detecting myocardial ischemia than typical treadmill ECG.[160] Even when exercise ECG is positive, it has been reported that the incidence of cardiac events is low if there is no abnormal wall motion on stress echocardiography.[161,162] In contrast, patients with a positive result for stress echocardiography are more likely to develop fatal or nonfatal cardiac events if untreated.[163,164]

#### e. Evaluation of the Cardiac Functional Reserve

It is possible to evaluate the cardiac functional reserve by stress echocardiography. Changes in cardiac pump function caused by myocardial ischemia can be detected in patients with chronic coronary heart disease. Doppler echocardiography, which is not dependent on detecting changes in cardiac morphology, is the preferred method for assessing stroke volume in patients with coronary heart disease and wall motion abnormalities,[165] and myocardial ischemia has been reported to alter the left ventricular outflow and inflow velocity waveforms.[166–168] However, these changes are nonspecific because they are not only influenced by the severity of ischemia, but also by various other factors such as the heart rate, preload, and afterload. Hence, these parameters are not a direct method of diagnosing myocardial ischemia and are less sensitive compared with detection of wall motion abnormalities.

### 5.2.4 Diagnostic Value of Various Stress Loading Methods

Currently, digitized imaging information obtained during stress echocardiography can be stored, allowing comparative evaluation of wall motion before and after loading, using images displayed in multiple windows on the same screen. The reliability of visual evaluation of wall motion was dramatically improved after this technique was introduced. The loading methods generally consist of exercise or pharmacological stress, with dobutamine or vasodilators being used as the pharmacological agents. Vasodilators include dipyridamole and adenosine, and these agents induce myocardial ischemia via the steal phenomenon. Thus, vasodilators are suitable for radionuclide myocardial perfusion imaging, which is excellent for detecting imbalances in blood flow distribution. However, induction of wall motion abnormalities by vasodilators is less frequent than with dobutamine,[169,170] so dobutamine is generally used for detection of coronary artery stenosis based on wall motion abnormalities. The accuracy of the various loading methods for detecting coronary heart disease is shown in **Table 18**.[171]

**Table 18. Diagnostic Accuracy of Various Stress Tests**

| | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Exercise stress ECG | 55–80 | 70–90 |
| Stress cardiac scintigraphy | 80–95 | 70–95 |
| Exercise stress echocardiography | 70–95 | 75–95 |
| Dobutamine stress echocardiography | 75–90 | 75–95 |
| Dipyridamole stress echocardiography | 45–80 | 80–95 |

(Reproduced from Koyanagi et al 1997,[171] with permission.)

## 5.3 Future Challenges

A problem with using stress echocardiography to diagnose coronary heart disease is that it is not possible to sufficiently obtain good images in all patients. Moreover, evaluation of wall motion is performed by visual analysis, resulting in

**Table 19. Recommendations and Levels of Evidence for Stress Echocardiography**

| | | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|---|
| **1. Diagnosis of coronary artery disease (CAD)** | | | | | |
| a) Evaluation of stable chest pain | Low possibility of CAD, ECG evaluation is possible, exercise stress test is possible | III | C | D | IVa |
| | Possibility of CAD is moderate or more | I | B | B | IVa |
| b) Evaluation of acute chest pain* | Possibility of CAD is moderate, no temporal ECG ST-T changes in the absence of myocardial necrosis | I | A | B | II |
| | High possibility of CAD, ECG ST-elevation | III | C | D | IVb |
| **2. Prediction of prognosis (risk evaluation)** | | | | | |
| Post unstable AP/non-STEMI without any ischemic symptoms, heart failure symptoms, or early schedule for cardiac catheterization* | | I | B | B | III |
| ACS, post-PCI, no symptoms, predischarge evaluation | | III | C | D | IVb |
| Post-PCI, ischemic symptoms (+) | | I | B | B | III |
| Post-PCI, no symptoms, <2 years since intervention | | III | C | C2 | IVb |
| **3. Evaluation of myocardial viability** | | | | | |
| Stenosis confirmed by CAG, suitable for revascularization | | I | A | A | III |

*Not chronic CAD. AP, angina pectoris; CAG, coronary angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence; STEMI, ST-elevation myocardial infarction.

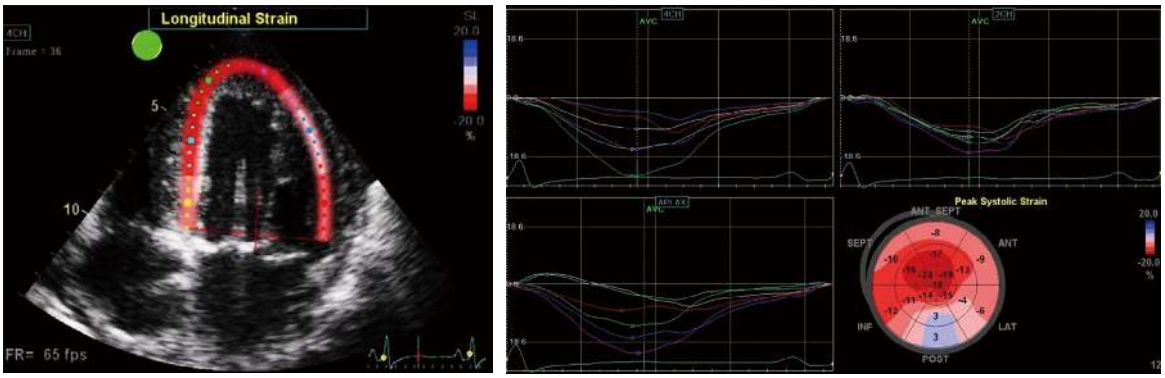



**Figure 3.** Myocardial strain echocardiography in an 84-year-old male patient with acute heart failure. (**Left**) Speckle-tracking analysis in the apical 4-chamber view. (**Right**) Longitudinal strain curves in all left ventricular segments. Peak systolic strains shown on the polar map are markedly decreased in the posterolateral segments. GLS was −12.4%.

a marked influence of the skill and subjectivity of the analysts. To overcome this problem, more objective methods have been developed for evaluation of wall motion abnormalities, such as real-time 3-dimensional echocardiography and new technologies such as 2- or 3-dimensional strain imaging,[172–175] and clinical application of these newer methods is increasing. Exercise echocardiography was added to the list of tests covered by health insurance in April 2012, and dobutamine stress echocardiography was included more recently in April 2018. In the future, it will be crucial to provide training so that doctors and medical sonographers become more familiar with this method in order to establish stress echocardiography as a routine examination. Recommendations and levels of evidence for stress echocardiography are shown in **Table 19**.

## 6. Myocardial Strain Echocardiography and Myocardial Contrast Echocardiography

### 6.1 Myocardial Strain Echocardiography

Myocardial strain echocardiography was developed for objective quantitative evaluation of regional myocardial motion by echocardiography, and analysis is performed by the tissue Doppler or speckle-tracking method. The tissue Doppler method has the problem of angle dependency (i.e., strain can only be evaluated in the direction of the ultrasound beam). In contrast, the speckle-tracking method allows analysis of strain in all regions of the left ventricle and can be applied for evaluation of the entire ventricle. It has been suggested that measurement of GLS can detect abnormalities of contractility that are not revealed by assessing LVEF, and it was recently reported that determination of GLS is useful for predicting the prognosis of various other diseases in addition to chronic coronary heart disease.

#### 6.1.1 Characteristics and Technical Aspects

With the speckle-tracking method, the unique echocardiographic speckle pattern of a myocardial region is automatically followed on successive images by pattern matching. This method allows evaluation of myocardial strain in all regions of the left ventricle.[176] In addition to the 2-dimensional method, a 3-dimensional speckle-tracking method that generates 3D images has become available in recent years.[177] Because the accuracy of the speckle-tracking method is highly dependent on image quality, it is important to obtain good images for accurate measurement of myocardial strain.

Strain is an indicator of the deformation of an object and is calculated as follows: (final length–initial length)/initial length. Myocardial strain is an index that was developed to apply this concept to deformation of the myocardium, and it is a measure of how far the regional myocardium stretches or shortens in a given direction. When the left ventricular myocardium is analyzed, the end-diastolic myocardial length is used as the "initial length". Peak systolic strain is used as an index of contractile function. A positive strain value indicates that the myocardium has stretched compared with its length at the end of diastole, and a negative strain value indicates that the myocardium has shortened.

When evaluation of regional wall motion is performed by conventional echocardiography, the change in wall thickness (i.e., movement of the myocardium in the radial direction on the short-axis image or in the transverse direction on the long-axis image) is evaluated by visual analysis. However, myocardial strain analysis also allows assessment of movement in the circumferential and longitudinal directions (**Figure 3**).

GLS represents the average longitudinal strain in all left ventricular segments, and was mentioned in the 2015 ASE/EACVI guidelines as a new index of global left ventricular systolic function.[131] This index is calculated as the average of the peak systolic strains derived from 3 apical views. The normal value is reported to be approximately −20%.[178] Because GLS has a negative value, confusion often occurs if attempts are made to express an increase or decrease in its value. Accordingly, reporting of absolute values is recommended.[131]

#### 6.1.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

Assessment of infarct size is important for predicting the prognosis as well as for diagnosis, and LVEF and the wall motion score index have traditionally been used for this

purpose. In patients with acute myocardial infarction, GLS provides a more accurate estimate of infarct size than these indices.[179] It is also useful for assessing the improvement of cardiac function and estimating the prognosis after acute myocardial infarction.[180–182] A study performed in patients with chronic ischemic cardiomyopathy showed that those with an absolute GLS <11.5% had a worse prognosis than the other patients.[183]

Recent reports have suggested that GLS is superior to LVEF for predicting the prognosis of patients with heart failure. In a prospective study of patients with chronic heart failure (including those with coronary heart disease), only GLS was a predictor of events according to multivariate analysis; LVEF and the E/e' ratio (an index of left ventricular filling pressure) were not predictors.[184,185] In addition, GLS was reported to be the best predictor of prognosis among all echocardiographic indices, even in patients who had heart failure with reduced LVEF, and was useful for risk stratification of patients with a reduced LVEF.[186] Therefore, the measurement of GLS is recommended in patients with chronic coronary heart disease, particularly those with heart failure.

Myocardial strain analysis is also useful for evaluating left ventricular dyssynchrony. Although it is difficult to predict the occurrence of high-risk ventricular arrhythmias in patients after myocardial infarction, a dyssynchrony index derived from strain analysis can predict the occurrence of such arrhythmias independently of LVEF.[187] In both experimental and clinical settings, it was found that myocardial layer-specific strain analysis could distinguish between no infarction, subendocardial infarction, and transmural infarction.[188,189]

### 6.1.3 Future Challenges

Standardization of GLS among vendors has been attempted, and has reached the point where such differences are less problematic.[178] On the other hand, differences in the determination of regional strain cannot be ignored,[190] and it is therefore recommended that comparison should be performed with the software of a single vendor for assessment of regional strain. Because the myocardium moves three-dimensionally, there are limitations to evaluation of myocardial strain based on 2D images, and 3D speckle-tracking analysis is desirable for more accurate evaluation. However, 3D imaging currently achieves lower spatial and temporal resolution than the 2D method, suggesting the need for improvement in the future.

## 6.2 Myocardial Contrast Echocardiography

Myocardial contrast echocardiography is a method of evaluating myocardial perfusion on echocardiograms by using the ultrasound enhancing agent. The ultrasound enhancing agent is a solution containing microbubbles, and the myocardial signal intensity is enhanced by these microbubbles flowing through the microcirculation. Although myocardial contrast echocardiography is not widely used, because no contrast media are covered by health insurance for evaluation of myocardial perfusion, it is not only possible to directly visualize the coronary microcirculation, but also to quantitatively evaluate myocardial blood volume, flow rate, and myocardial blood flow.

### 6.2.1 Characteristics and Technical Aspects

Microbubbles in the ultrasound enhancing agent (air or fluorocarbon gas) pass through the capillaries in the same way as red blood cells, so the myocardial contrast enhancement obtained by this method is an indicator of the myocardial microcirculation (mainly the capillary bed).[191]

When intracoronary injection is performed, myocardial contrast enhancement can easily be obtained. However, myocardial contrast enhancement cannot be obtained in the standard echocardiographic setting when peripheral intravenous injection is performed. This is because only a small number of microbubbles enter the coronary microcirculation after peripheral injection and the ultrasound beam itself destroys bubbles in the microcirculation. Accordingly, an imaging method was devised to minimize

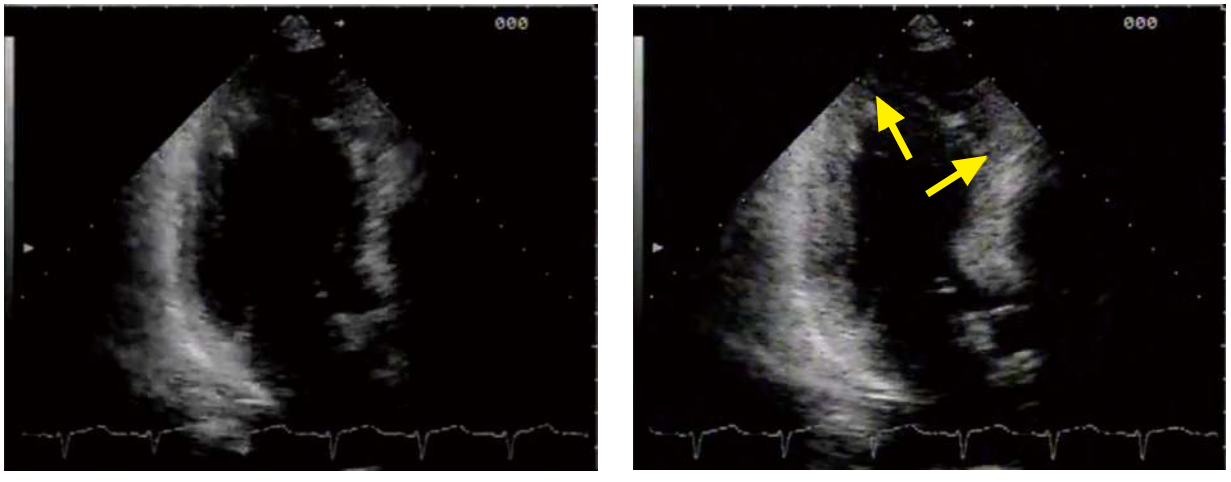


**Figure 4.** Myocardial contrast echocardiography in a 71-year-old female patient with acute anterior myocardial infarction. Intracoronary myocardial contrast echocardiography was performed after reperfusion of the left anterior descending artery by PCI. (**Left**) Before contrast injection into the left coronary artery. (**Right**) After contrast injection. Although coronary angiography showed TIMI 3 flow after PCI, a contrast defect due to the no-reflow phenomenon was observed in the apex (arrows).

**Table 20. Recommendations and Levels of Evidence for Strain- and Contrast Echocardiography for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Prediction of the prognosis using GLS | I | B | B | IVa |
| Assessment of myocardial viability | IIa | C | B | IVb |
| Evaluation of myocardial microvascular damage | IIa | C | B | IVb |

COR, class of recommendation; GLS, global longitudinal strain; GOR, grade of recommendation; LOE, level of evidence.

destruction of the microbubbles by intermittent transmission of an ultrasound pulse. In a clinical study, evaluation of perfusion by the intermittent mode yielded similar results to those of myocardial scintigraphy.[192] A multicenter study also showed that the results of myocardial contrast echocardiography and myocardial scintigraphy were consistent.[193]

Subsequently, high-sensitivity imaging methods were developed using multiple ultrasound pulses, such as the pulse inversion method, allowing visualization of myocardial perfusion with low acoustic pressure ultrasound that did not destroy microbubbles.[194] When using this mode, there is no need for intermittent imaging and real-time evaluation of myocardial perfusion is possible. Real-time myocardial contrast echocardiography also allows simultaneous observation of left ventricular wall motion, which is advantageous for making a diagnosis of ischemia. However, use of a fluorocarbon gas contrast agent is essential to obtain adequate signals at a low acoustic pressure.

### 6.2.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

Myocardial contrast echocardiography is useful for quantitative assessment of the coronary microcirculation by the method of Wei et al.[195] If the transmitted ultrasound pulse has a sufficiently strong acoustic pressure to completely destroy the microbubbles at the time of stable blood concentration, gradual extension of the interval for intermittent transmission allows more bubbles to flow into the ultrasound beam width until a plateau is reached. The relationship between the intensity of myocardial contrast enhancement and the ultrasound pulsing interval is approximated by the function $y=A(1-e^{-\beta t})$, where y is the contrast signal intensity, t is the pulsing interval, A is the plateau level of contrast signal intensity, and $\beta$ is the reciprocal of the pulsing interval T that reaches the plateau value A. The curve that can be drawn from this relation is called a replenishment curve.

Because "A" derived from this function reflects the myocardial blood volume and "$\beta$" reflects the flow rate, the product of these values ($A\times\beta$) closely correlates with myocardial blood flow.[195] Myocardial contrast echocardiography is possible with the real-time method as well as the intermittent method.[196] In particular, noninvasive assessment of flow rate $\beta$ is difficult using any method apart from myocardial contrast echocardiography, and it has been reported that the $\beta$ reserve correlates well with CFR obtained by the Doppler guidewire method.[197]

Myocardial contrast echocardiography visualizes the microcirculation, and can also estimate myocardial viability. In some patients with acute myocardial infarction, a contrast defect (the "no-reflow" phenomenon) is observed after reperfusion (**Figure 4**). In such cases, improvement of cardiac function in the chronic phase cannot be expected.[198] Moreover, hemorrhagic infarction occurs at a high frequency,[199] and the long-term prognosis is poor.[200] It has been reported that the $A\times\beta$ value derived from the replenishment curve can be used to estimate myocardial viability with greater accuracy than dobutamine stress echocardiography or myocardial scintigraphy in patients with chronic coronary heart disease.[201] Recommendations and levels of evidence for strain and contrast echocardiography are shown in **Table 20**.

### 6.2.3 Future Challenges

Currently, the lack of ultrasound enhancing agents that can be used to assess myocardial perfusion is an obstacle to widespread adoption of myocardial contrast echocardiography. However, given that this method can not only directly visualize the myocardial microcirculation, but also makes it possible to evaluate previously unmeasurable indicators such as $\beta$, it is expected to be used clinically when a ultrasound enhancing agent for myocardial perfusion is approved in the future.

## 7. Cardiac Radionuclide Imaging

### 7.1 Myocardial Perfusion Imaging

#### 7.1.1 Features and Evidence

Cardiac radionuclide imaging is a noninvasive functional imaging method for patients with coronary heart disease and is widely used for diagnosis, evaluation of severity, determination of treatment strategies, and assessment of the prognosis. With cardiac radionuclide imaging, myocardial blood flow can be readily evaluated during exercise or pharmacological stress. Particularly, a major feature is that diagnosis of myocardial ischemia is possible by combining radionuclide imaging with an exercise test. Even if exercise testing is impossible or contraindicated, stress testing with a vasodilator allows safe diagnosis of coronary heart disease and risk assessment. In patients with coronary heart disease, the pretest probability based on the Bayes theorem should be considered when selecting the basic diagnostic procedures.

Both stress and resting myocardial perfusion SPECT have been widely used for diagnosis of coronary heart disease in routine clinical practice since the 1970s. Myocardial perfusion SPECT has been shown to be particularly useful in patients with a moderate pretest probability. Prognostic studies involving thousands of patients have been performed in Western countries and Japan, resulting in accumulation of extensive evidence on the usefulness of

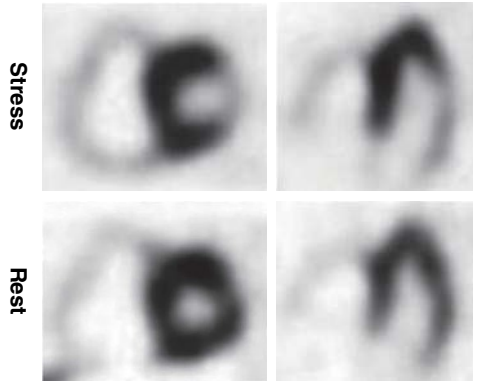



**Figure 5.** Exercise stress $^{99m}$Tc myocardial perfusion SPECT in a case of left circumflex territorial ischemia. Stress-induced ischemia was observed in the lateral wall, which was filled on the rest image. This finding is compatible with the left circumflex coronary territory.

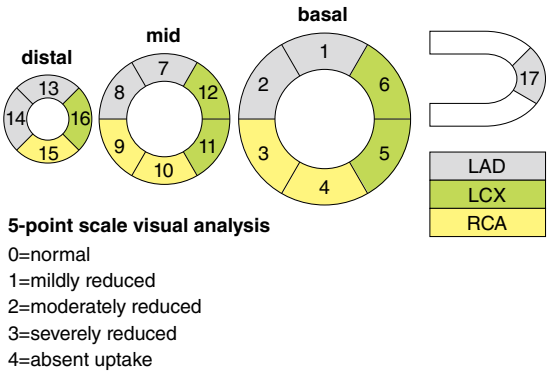



**Figure 6.** A 17-segment model and 5-point scale semiquantitative visual analysis: 0=normal 1=mildly reduced 2=moderately reduced 3=severely reduced; 4=absent uptake. LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery.

myocardial perfusion SPECT for diagnosis and prognostication.

Radionuclide imaging makes it possible to noninvasively obtain information on physiological function with a trace dose of a radiopharmaceutical while not using contrast medium. Hence, this noninvasive modality can be the first choice for patients with CKD. Exposure to radiation during myocardial perfusion SPECT has been significantly reduced by the introduction of technetium (Tc)-99 m-labeled preparations with a short half-life. On the other hand, cardiac radionuclide imaging is less effective for obtaining morphological information in comparison with other imaging modalities. Accordingly, fusion imaging is performed for comprehensive investigation of pathology by appropriately combining radionuclide imaging with other methods according to the patient's condition.[202] Albeit there is still insufficient evidence, some reports indicate that the diagnostic value of fusion imaging is higher than that of single imaging modalities, and that it is useful for both predicting the prognosis and selecting treatment.[203,204] Cardiac radionuclide imaging is currently in widespread clinical use and there is established evidence for its use in the evaluation of myocardial blood flow and myocardial viability.

### 7.1.2 Rest and Stress Myocardial Perfusion Imaging

The most widely used cardiac radionuclide imaging modality for diagnosis and selection of treatment strategies for coronary heart disease is stress and rest myocardial perfusion SPECT (**Figure 5**). Among the various radiopharmaceuticals, Tl-201 is widely used in Japan, as well as Tc-99 m MIBI and Tc-99 m Tetrofosmin, which have shorter half-lives and achieve good image quality. For stress loading, exercise (treadmill or bicycle ergometer) is used whenever possible, whereas vasodilators (adenosine, adenosine triphosphate [ATP], or dipyridamole) are used only if exercise cannot be performed or is contraindicated. In Japan, use of adenosine for stress testing is covered by health insurance. (Note: ATP and dipyridamole are not covered for use in stress myocardial perfusion SPECT by Japanese health insurance.) When stratified by the type of loading, the sensitivity and specificity of exercise myocardial perfusion SPECT for detection of significant coronary stenosis was reported to be 82–88% and 70–88%, respectively, whereas stress myocardial perfusion SPECT using vasodilators has a sensitivity of 88–91% and a specificity of 75–90%.[8,205–213]

Recently, use of a gamma camera for the heart using cadmium–zinc–telluride semiconductors as the gamma ray detector has become popular. Its sensitivity is reported to be 84–87% and its specificity is 62–86% for lesions in the left anterior descending artery, 75–84% and 84–93% for lesions in the left circumflex artery and 74–80% and 77–88% for lesions in the right coronary artery.[214–216]

ECG-gated acquisition has recently become popular as a standard imaging procedure, allowing concurrent analysis of both myocardial blood flow and cardiac function. ECG gating can be used to assess left ventricular wall motion, systolic wall thickening, left ventricular volume, LVEF, left ventricular diastolic function, and left ventricular synchrony. The following are indicators of high-risk patients, such as those with multivessel disease or left main trunk lesions: decreased wall motion with stress that reflects stunned myocardium; LVEF <45% at rest or after stress; reduction of LVEF by >5% after stress; transient left ventricular dilation (dilation by ≥10% vs. rest); increased pulmonary accumulation of the radionuclide; and visualization of the right ventricle.[217–221]

Myocardial perfusion SPECT has prognostic value in patients with a moderate risk of coronary heart disease. Based on this classification, large-scale registry studies, clinical studies, and meta-analyses have demonstrated an extremely low incidence of cardiovascular death and nonfatal myocardial infarction when stress myocardial perfusion SPECT findings are within the normal range.[222,223] In addition, the incidence of cardiac events increases in proportion to the stress perfusion defect score calculated from SPECT images, suggesting its usefulness for predicting the prognosis (**Figure 6**).[223–226] The incidence of cardiac events increases with an increase in the extent of ischemic myocardium, and the prognosis improves together with a decrease in ischemic myocardium after coronary revascularization. Therefore, demonstration of myocardial ischemia affecting >10% the left ventricle on stress myocardial perfusion SPECT is recommended as the indication for revascularization.[127,226,227]

### 7.1.3 Detection of Myocardial Viability

Cardiac radionuclide imaging is useful for assessing myocardial viability in patients with coronary heart disease. The presence of ischemia and the extent of blood flow reduction are usually judged by myocardial perfusion SPECT, and a high diagnostic accuracy has been shown. Tl-201 is used to assess viability based on cell membrane and Na/K pump function, whereas Tc-99 m assesses mitochondrial function.[228] It has been reported that quantitative evaluation (% uptake) improves the accuracy of evaluating myocardial viability, and the threshold value is usually set at 50–60%.[229] There have been many reports that Tl-201 myocardial perfusion SPECT is useful for predicting the improvement of wall motion after revascularization.[230,231] Although there are some contradictory opinions, the diagnostic sensitivity was reported to be similar or better than that of dobutamine stress echocardiography (but specificity is inferior), with Tl-201 myocardial perfusion SPECT being reported to show a sensitivity of 86% and a specificity of 59%.[232] When stress Tl-201 myocardial perfusion SPECT is performed, residual viable myocardium may be underestimated by conventional delayed imaging because of insufficient redistribution, so small additional doses of the radionuclide are given or 24-hour imaging is performed as a countermeasure.[229–232] Tc-99 m myocardial perfusion SPECT was reported to show a sensitivity of 81% and a specificity of 66%.[233] To prevent underestimation, sublingual nitroglycerin is considered effective.[233,234] If stress myocardial perfusion scintigraphy cannot adequately assess myocardial viability, $^{18}$F-FDG-PET is an alternative imaging method for this purpose.

### 7.1.4 Radiation Exposure With Cardiac Radionuclide Imaging

It is necessary to optimize test methods and protocols by considering both the usefulness for diagnosing coronary heart disease and the risk of radiation exposure with cardiac radionuclide imaging. Tc-99 m-labeled myocardial perfusion radiopharmaceuticals have a short half-life of 6 hours, so it is possible to reduce radiation exposure by using these agents for scintigraphy. The stress and resting protocol generally used in Japan involves administration of doses from 740 to 1,110 mSv, the whole-body dose is 6–9 mSv.[235] Therefore, use of Tc-99 m-labeled radiopharmaceuticals is recommended from the perspective of reducing exposure to radiation. However, Tl-201 is recommended if intestinal accumulation was high during previous Tc-99 m myocardial perfusion imaging. In order to reduce radiation exposure, it is also effective to promote excretion of the radionuclide in the urine by increased intake of water after imaging.[236] Gamma cameras equipped with a dedicated semiconductor detector for the heart have become increasingly available in recent years, and show 5–6-fold higher gamma ray sensitivity than standard cameras, which is also useful for minimizing radiation exposure.[214] It has been reported that performing a stress-only protocol that omits resting images is useful when a low-dose stress/resting protocol and stress imaging using Tc-99 m (taking advantage of its high sensitivity) are normal.[237–239]

## 7.2 Stress Myocardial Perfusion Imaging

### 7.2.1 Indications

In the setting of chronic coronary heart disease, stress myocardial perfusion imaging is indicated for detecting the presence or absence of ischemia, predicting the prognosis and risk stratification based on ischemic burden, determining the indications for revascularization, judging effects of treatment, and predicting the prognosis after initiation of treatment.

#### a. Detection of Ischemia

When stress myocardial perfusion imaging is performed to detect ischemia, the best indication is typical angina pain with an intermediate or high pretest probability.[240,241] If the reversible defect identified by perfusion imaging, this means moderate or high risk (see next section **7.2.2**). Because exercise ECG cannot be used for diagnosis of ischemia in patients with left ventricular hypertrophy with ST depression or in those taking digitalis, stress myocardial perfusion imaging is a suitable option in such cases. Agents used for pharmacological stress include dipyridamole, ATP, and adenosine. Adverse reactions to adenosine are minor, but the incidence is high,[242] and extracardiac accumulation in the liver and gastrointestinal tract is greater than with exercise, so artifacts are often problematic. Therefore, concomitant low-level exercise loading is also recommended because fewer adverse reactions and improvement of image quality are expected.[241,243] Adenosine receptors are competitively inhibited by xanthine derivatives such as aminophylline and caffeine, and intake of caffeine-containing products should therefore be avoided for at least 12 hours before an adenosine stress test is performed.[244] If adenosine cannot be used (e.g., in patients with bronchial asthma), a dobutamine stress test is alternatively performed.[245] Atropine may also be used in combination with dobutamine in patients on $\beta$-blockers to avoid underloading; the sensitivity and specificity of this method are 85% and 72%, respectively, with a diagnostic accuracy of approximately 83%.[246]

Identification of ischemia is also an indication when severe calcification in the coronary arteries is detected, such as on chest and CCTA. Because coronary artery calcification and ischemia are positively correlated,[247,248] and a CACS ≥400 corresponds to a moderate pretest probability, stress perfusion imaging should be considered. Even if the findings of stress perfusion imaging are normal, severe calcification with a CACS ≥1,000 is associated with a moderate incidence of severe coronary artery lesions requiring revascularization.[249] Therefore, coronary angiography is indicated in such cases if the patient has chest pain. In contrast, ischemia is rare in asymptomatic patients with a CACS ≤100,[247,250] and perfusion imaging is not indicated. Recently, SPECT-CT has become popular. Because visual assessment of the severity of coronary artery calcification on low-dose CT scans obtained for attenuation correction is well correlated with the CACS, assessing coronary artery calcification is recommended when CT scans are taken for attenuation correction.[251]

With regard to diagnosis of ischemia in asymptomatic patients, stress myocardial perfusion imaging may be considered for high-risk patients with multiple coronary risk factors,[252] patients with decreased exercise tolerance,[253] and patients with an elevated CACS,[248,254] if they have a high pretest probability, but it is not indicated for patients with a moderate to low pretest probability.[254] The CACS is useful for risk stratification in relation to the long-term prognosis, even in asymptomatic patients,[253] and measurement of CACS may be considered first in some cases.[127] In

the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, adenosine stress myocardial perfusion imaging was performed in 1,123 asymptomatic patients with type 2 diabetes and abnormal findings were obtained in 22%, with the frequency of moderate or severe perfusion defects increasing 5-fold as the disease duration became longer.[255] In a 3-year prognostic study, the extent of myocardial ischemia was significantly reduced by drug therapy,[256] demonstrating the usefulness of severity assessment and follow-up with stress myocardial perfusion imaging. Investigation of ischemia may be indicated if there are ST-T changes on ECG or wall motion abnormalities on echocardiography. However, there is no clear evidence for this, and further studies are needed in the future.

#### b. Significance in the Diagnosis of Chronic Coronary Heart Disease

There have been remarkable recent improvements in the accuracy of various imaging modalities for diagnosing chronic coronary heart disease. CCTA, MRI, stress echocardiography, myocardial perfusion SPECT, and PET each have advantages and disadvantages, and many reports on their diagnostic accuracy have been published. Although there may be some variation among reports, the diagnostic accuracy of the modality in which each facility has expertise is probably close to the generally reported level of accuracy. Regarding the diagnostic accuracy of stress myocardial perfusion imaging, the sensitivity and specificity are estimated to be 73–92% and 63–87%, respectively.[205,257,258] There is generally no difference in specificity between pharmacological and exercise stress testing. However, patients who cannot perform sufficient exercise are typically tested using vasodilators, which makes the specificity of vasodilator testing higher because patients who cannot exercise adequately are more likely to have coronary heart disease.[205,206,259] Because adenosine was administered at a dose of 140 $\mu$g/kg/min in the studies that obtained this result, the sensitivity at 120 $\mu$g/kg/min (the dose used in Japan) is probably equivalent to that of exercise testing.[260,261] It should also be noted that these studies were conducted using Tl-201, which means that the sensitivity of testing with Tc-99m agents may be lower because its myocardial extraction decreases at high rates of blood flow. No clear evidence has been obtained so far, but this is a point to consider when interpreting images. Diagnostic accuracy has conventionally been calculated by comparison with anatomical stenosis of ≥50–70% on coronary angiography as the gold standard, but anatomical stenosis is not always consistent with ischemia that reflects functional stenosis. Therefore, there have recently been an increasing number of studies in which diagnostic accuracy was examined by severe stenosis (≥70%), or using a FFR <0.8 for moderate stenosis (30–70%) as the gold standard. FFR <0.8 was used as a criterion for significant coronary lesions in the EVINCI study, which enrolled patients with a moderate pretest probability.[262] EVINCI compared diagnostic accuracy among CCTA, PET, SPECT, MRI, and echocardiography. Overall, CCTA showed the highest diagnostic accuracy with an area under the curve (AUC) of 0.91, sensitivity of 91%, and specificity of 92%, whereas SPECT achieved an AUC of 0.74, sensitivity of 74%, and specificity of 73%. When only patients with good-quality images were assessed, these numbers improved to a sensitivity of 81%, specificity of 86%, and diagnostic accuracy of 84%, which means that the diagnostic accuracy is as good as that of PET (which has the most stable diagnostic accuracy).[262] Given that the quality of SPECT images acquired in Japanese patients usually corresponds to "good image quality" in Western countries, except when artifacts occur, the diagnostic accuracy of SPECT may be close to that of PET in Japanese patients. When CCTA, PET, and SPECT were compared in patients with suspected coronary heart disease, using FFR <0.8 as an indicator of significant coronary lesions, SPECT showed the lowest sensitivity of 57% vs. 90% for CCTA and 87% for PET, but SPECT had the highest specificity of 94% vs. only 60% for CCTA and 84% for PET. The diagnostic accuracy of CCTA, SPECT, and PET was 74%, 77%, and 85%, respectively.[263–265] When diagnosis is based on the FFR, PET has the highest diagnostic accuracy and achieves stable results, and the low sensitivity of SPECT needs to be taken into consideration. In a study using a semiconductor camera, the sensitivity, specificity, and accuracy were low (52%, 68%, and 58%, respectively) when a significant lesion was defined as corresponding to ≥75% stenosis on coronary angiography. However, when "≥90% stenosis" or "<90% and ≥50% stenosis" combined with FFR <0.8 was adopted as the definition of a significant lesion, the sensitivity, specificity, and diagnostic accuracy improved to 77%, 91%, and 84%, respectively.[237] Thus, SPECT does not always reflect anatomical stenosis, but can detect flow-limiting functional stenosis with a high level of accuracy.[237]

Because SPECT images display the relative blood flow distribution, a weakness of this method is low detection rates for balanced ischemia caused by multivessel disease, etc.[266] However, quantitative evaluation of myocardial blood flow has become possible with the development of semiconductor cameras.[267,268] In studies of dynamic imaging using Tl-201, when a myocardial flow reserve (MFR) ≤1.5 was used as the cutoff value for detection of left main trunk or triple-vessel disease, favorable results were obtained with a sensitivity, specificity, and diagnostic accuracy of 86%, 78%, and 80%, respectively.[269] Quantitative evaluation of myocardial blood flow by SPECT is not suitable for routine clinical practice because of its complexity, but it allows accurate diagnosis of even balanced ischemia (which is often underestimated by conventional SPECT) in appropriate patients. Compared with MRI, SPECT has a lower sensitivity but higher specificity. MRI is considered to show a high negative predictive value, but has a low specificity.[270–272] It should also be kept in mind that studies of the diagnostic accuracy of stress myocardial perfusion imaging were conducted after withdrawal of antianginal drugs, so the diagnostic accuracy (particularly the sensitivity) of this modality could be lower if testing is performed without discontinuing these drugs.[273,274]

### 7.2.2 Predicting the Prognosis and Risk Stratification

There is considerable evidence on using stress myocardial perfusion imaging for predicting the prognosis. The amount of ischemic myocardium, based on the severity and extent of ischemia, is better correlated with prognosis than the severity of coronary heart disease assessed by coronary angiography,[275] and is also strongly correlated with "hard events" such as nonfatal myocardial infarction and cardiac death.[227,276] Although the incidence of events is lower in Japanese patients than in Westerners, a similar trend was confirmed by a prospective multicenter prognosis study (J-ACCESS study) with over 4,000 subjects.[223] When stress myocardial perfusion imaging is normal, the prognosis is

good and the annual hard event rate is only approximately 0.6%,[277] and even lower in the Japanese population.[278] If SPECT is normal, the annual cardiac event rate is <1%, even in patients with moderate coronary stenosis on coronary angiography. This may be a reason for deciding to defer revascularization when considering whether or not revascularization should be performed. However, the predictive value of SPECT is lower than that of CFR or FFR in patients with multivessel disease.[279,280] On the other hand, the high-risk SPECT findings are associated with a poor prognosis. An observational study of 2,686 patients revealed that patients with moderate or severe ischemia (equivalent to ≥10%) and a low LVEF (LVEF <30%) had an annual mortality rate 50-fold higher than patients with normal results.[281] In general, the high-risk findings include fixed/reversible defects in multivessel territories, transient ischemic dilatation, LVEF <45%, and high pulmonary accumulation during stress loading. These findings are useful for predicting the prognosis.

The PROMISE study was a prospective randomized trial performed at 193 centers that allocated 10,003 patients with suspected stable angina to CCTA or functional testing (exercise ECG in 10.2%, stress myocardial perfusion scintigraphy in 67.5%, and stress echocardiography in 22.4%), revealing no difference between groups with regard to the 2-year event rate for myocardial infarction, death, or unstable angina/complications requiring hospitalization.[282] However, coronary angiography and revascularization were more frequent in the CCTA group. The population studied in this investigation had a relatively favorable 2-year event rate of 3%, with nearly half of the events being hospitalization for unstable angina and a low frequency of hard events, which means that they were generally low-risk patients.

Thus, CCTA tends to overestimate the need for further intervention in low-risk patient populations, and it is not recommended from the perspective of cost-effectiveness.

A multicenter randomized controlled trial (IAEA-SPECT/CTA study) that compared CCTA and stress myocardial perfusion SPECT in patients with a moderate pretest probability who were asymptomatic or had mild chest pain showed 49% reduction of patients undergoing subsequent evaluation in the SPECT group, indicating that SPECT can be recommended for patients with a moderate pretest probability in view of its cost-effectiveness.[283] The J-COMPASS study investigated the prognosis of 2,878 Japanese patients with suspected or confirmed stable angina, who underwent CCTA, stress perfusion imaging, or coronary angiography as the initial test. There was no difference in the incidence of MACE between the patients undergoing CCTA and those having stress perfusion imaging, but the frequency of undergoing coronary angiography was 2.7-fold higher in patients initially undergoing CCTA. The revascularization rate was also highest in patients undergoing coronary angiography (odds ratio: 5.36), and was still higher in those having CCTA (odds ratio: 1.62) than in those undergoing stress perfusion imaging.[284] The results of this study do not seem to recommend initial coronary angiography for patients with stable angina, and it was also shown that morphological assessment is more likely to lead to revascularization than functional assessment.

The COURAGE study compared outcomes in 2,287 patients with significant stenosis who were randomized to 2 groups (optimal medical therapy group or PCI followed by medical therapy group), and found no differences in hard event rates.[285] However, the nuclear COURAGE substudy involving 105 patients with moderate to severe ischemia who underwent SPECT before treatment and approximately 1 year later showed that cardiac events were halved if ischemia improved by ≥5% after starting either treatment.[226] A similar predictive value was demonstrated in a single-center Japanese investigation, which revealed that improvement of ischemia by ≥5% was associated with subsequent prognostic improvement.[286] Furthermore, a multicenter study (J-ACCESS4 study) of 114 patients treated with medical therapy or revascularization showed that those with ≥5% improvement in the extent of ischemic myocardium had a significantly lower rate of cardiac events than those without such improvement.[287]

In addition to interpretation of imaging findings, the clinical information is important for predicting the prognosis with SPECT. In particular, diabetes mellitus and CKD are significant adverse prognostic factors. In a Japanese study of 485 patients with type 2 diabetes who underwent SPECT (J-ACCESS2 study), a summed stress score (SSS) >9 and a low eGFR were significant predictors of events.[288] In another study of 529 patients with CKD who underwent SPECT (J-ACCESS3 study), SSS ≥8, eGFR <15 mL/min/1.73 m$^2$, and C-reactive protein ≥0.3 mg/dL were significant predictors of events.[289] Cardiac function is also an important prognostic indicator. According to data from the J-ACCESS study, the incidence of cardiac events was 5.6-fold higher in patients with a LVEF <45% compared with those with LVEF ≥45%.[223] Thus, an equation for predicting the incidence of cardiac events based on the presence/absence of diabetes mellitus, eGFR, LVEF, age, and sex has been derived, based on the database for the normal Japanese population and the results of the J-ACCESS study.[290] The equation can be used to calculate the 3-year expected incidence of the composite endpoint of myocardial infarction, cardiac death, and heart failure requiring hospitalization, and it is useful for selection of treatment strategies and for providing information to patients.

An association between the findings on stress testing and the prognosis has been noted in several studies. Ischemic ST depression is rarely seen during pharmacological stress testing using vasodilators (<1%).[291,292] Although there have been reports that patients with normal perfusion images have a good prognosis, even if ST depression occurs,[291–294] in patients with ST depression during pharmacological loading, concomitant perfusion defects have a higher likelihood of indicating severe CHD.[292,295] If ST depression is induced during the test, there is a high possibility of severe coronary heart disease even when perfusion is normal,[296] and some reports indicate that the frequency of future cardiac events is high in such cases.[292,296] Careful management of the patient is recommended when ST depression is observed during pharmacological stress testing, irrespective of whether or not perfusion images are normal. With regard to ischemic electrocardiographic changes during stress tests, a subanalysis of the J-ACCESS study showed that patients with ischemic electrocardiographic changes and a reversible perfusion defect on exercise testing had a higher incidence of cardiac events, while patients without a reversible perfusion defect had fewer events.[297] Changes in the heart rate during pharmacological loading also have prognostic significance. The heart rate usually increases by ≈30 beats/min in stress tests using vasodilators.

When the increase is smaller than about 20 beats/min, however, there is a high risk of cardiac events and death, even with normal perfusion. Hence, the change in the heart rate is considered an independent predictor and attention should be paid to it.[298,299] It should also be noted that β-blockers and caffeine will blunt the increase in heart rate.

### 7.2.3 Judgment of Indications for Revascularization

The primary indications for myocardial perfusion imaging before revascularization are assessment of the severity of ischemia, risk stratification and predicting the prognosis, detection of ischemia in patients with cardiac dysfunction, and evaluation of viability (including detection of stunned and hibernating myocardium).[207] There is no indication for revascularization in the absence of ischemia, whereas the prognosis worsens with the extent of ischemic myocardium in the presence of ischemia, making it important to quantitatively or semiquantitatively assess the amount of ischemic myocardium. Particularly, when ischemia affects >10% of the total myocardium, the prognosis is poor with medical therapy and revascularization is indicated for improvement. Conversely, if <10% of the myocardium is ischemic, performing revascularization often worsens the prognosis and medical therapy is recommended.[229] Similar results were obtained by subanalysis of the J-ACCESS study.[300] In patients with cardiac dysfunction, detection of ischemic cardiomyopathy as the underlying disease and evaluation of myocardial viability are of importance. Dobutamine stress echocardiography, MRI, SPECT, and PET are mainly used to evaluate myocardial viability.

Among them, $^{18}$F-FDG-PET is the most accurate modality for predicting functional improvement in patients with cardiac dysfunction, and it is currently considered the gold standard.[230,301,302] When stress myocardial perfusion imaging is performed (with Tl-201 or Tc-99 m), a reversible perfusion defect or ≥50% accumulation relative to the normal region is judged to indicate the existence of viable myocardium.[234,303–305] With Tl-201 imaging, even if a fixed defect is recognized, redistribution may be noted in approximately 20% by re-infusion of the radionuclide or by imaging after 24 hours, and the sensitivity of assessing myocardial viability is improved. Revascularization does not improve the prognosis in the absence of viable myocardium, whereas prognosis is favorable after revascularization of viable myocardium, even without improvement of LVEF.[306] The STICH study indicated that evaluation of myocardial viability could identify patients who would benefit from CABG.[307] Patients who show remodeling without viable myocardium (left ventricular end-systolic volume index [LVESVI] ≥84 mL/m$^2$) have the worst prognosis,[308] and progression of remodeling should also be noted. Usefulness of evaluating myocardial viability by $^{18}$F-FDG-PET was not demonstrated in patients with poor cardiac function in the PARR-2 study.[309] However, subanalysis of the study showed that revascularization improved the prognosis in patients with a large area of hibernating myocardium.[310] Therefore, if more than 10% of viable myocardium remains, revascularization is expected to improve survival.[307,311] It has been reported that the left ventricular end-systolic volume is the only predictor of survival in coronary heart disease patients with viable myocardium and poor cardiac function, regardless of whether revascularization is performed, and that survival is unfavorable after revascularization in patients with advanced remodeling despite the presence of viable myocardium.[312]

Myocardial perfusion imaging plays an important role in determining the indications for revascularization when CCTA and coronary angiography show moderate stenosis (≈30–70%). As noted above, the amount of ischemic myocardium closely correlates with the incidence of cardiac events,[227,276] so revascularization should be actively considered when ischemic myocardium exceeds 10%. When invasive assessment of moderate stenosis is performed, revascularization should be considered if CFR is <2.0 or FFR is <0.8, but the CFR and FFR data are often inconsistent.[313] Since the results of the FAME study[314] and FAME 2 study[315] were published, FFR has been used as the gold standard for revascularization and is recommended in guidelines,[316,317] but CFR <2.0 is associated with a poor prognosis even in patients whose FFR is maintained.[318] The cutoff value of FFR for ischemia is 0.75.[319] However, further research is necessary because it was reported that the long-term prognosis of patients in the "gray zone" (FFR: 0.75–0.80) was better with revascularization,[320] and another study showed that deferring revascularization when FFR was >0.75 led to a comparable result to deferring revascularization when FFR was >0.8.[321] CFR is influenced by the peripheral circulation and is better correlated with the results of myocardial perfusion imaging than FFR, which is not influenced by peripheral factors.[322,323] Finally, in an observational study of 5,340 patients with multivessel disease, the prognosis was better when revascularization was guided not by coronary angiography alone but by ischemia on perfusion imaging.[323]

### 7.2.4 Evaluation of the Response and Prognosis After Treatment

Myocardial perfusion imaging has been used to assess the efficacy of revascularization.[324–326] It can determine improvement in cardiac function, as well as the ischemic burden.[327] It is also useful for assessing ischemia in the territory of the treated vessel at 6 months after PCI, and for estimating restenosis and residual stenosis.[328] More than half of all patients with ischemia are asymptomatic after PCI, and their prognosis is better than that of symptomatic patients. Despite this, the extent of coronary disease is closely related to the extent of ischemia.[328] The criteria for appropriate use do not recommend the performance of stress myocardial perfusion imaging in asymptomatic patients within 2 years after PCI.[240] However, routine myocardial perfusion imaging at 5 years after PCI revealed abnormal findings in 60% of patients and most were in remote areas, suggesting new lesions.[329] In patients with abnormal findings, MACE and hard events are more frequent, regardless of whether the patients have symptoms. Therefore, myocardial perfusion imaging may be considered at 5 years after PCI, even if the patient has no symptoms.[329]

In the COURAGE nuclear substudy, stress myocardial perfusion imaging was performed before treatment and 0.5–1.5 years after treatment. No residual ischemia at the second examination was associated with no events for at least the subsequent 4 years, but an increase in cardiac events correlated with the level of residual ischemia. Hence, this method is useful for assessing the efficacy of treatment (residual ischemia) and for predicting the prognosis after treatment.[226] In that study, the cardiac event rate halved when ischemic myocardium was reduced by ≥5%, demonstrating that the extent of improvement in ischemia is closely related to the prognosis.[226] Even with medical

**Table 21. Recommendations and Levels of Evidence for Myocardial Perfusion Imaging for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Uninterpretable ECG (complete left bundle branchi block, pacing and preexcitation syndrome are suitable for vasodilation stress) | I | B | B | I |
| Abnormal stress ECG | I | B | B | I |
| More than intermediate pretest probability case with typical chest pain | I | B | B | I |
| Diagnosis of presence and location of residual ischemia in known CAD | I | B | B | I |
| Diagnosis of location in myocardial infarction cases | I | B | B | I |
| Decision-making of coronary intervention therapy | I | B | B | I |
| Atypical chest pain cases with ≥ intermediate pretest probability or CACS ≥400 | IIa | B | C1 | II |
| Functional assessment of intermediate stenotic (40–75%) lesion | IIa | B | C1 | II |
| Assessment of interventional therapy | IIa | C | C1 | III |
| Pharmacological stress in case of intermediate pretest probability without appropriate exercise tolerance | IIa | C | C1 | III |
| Asymptomatic cases with DM or strong family history of CAD or CACS ≥400 | IIb | C | C2 | IVb |
| Assessment of ischemia in cases of low pretest probability with chest pain | IIb | C | C2 | IVb |
| Assessment after 5 years in cases of revascularization | IIb | C | C2 | IVb |
| Less than intermediate pretest probability cases without symptom | III | C | D | V |
| Routine assessment within 2 years after revascularization | III | C | D | V |

CACS, coronary artery calcium score (Agatston score); CAD, coronary artery disease; COR, class of recommendation; DM, diabetes mellitus; GOR, grade of recommendation; LOE, level of evidence.

treatment, the prognosis can also be improved if there is a marked reduction in the extent and severity of ischemia. However, the rate of achieving ≥5% reduction of ischemic myocardium was significantly higher in the PCI group, and it can be assumed that the prognosis is improved by prior PCI when the volume of ischemic myocardium is medium or large. Recommendations and levels of evidence for myocardial perfusion imaging are shown in **Table 21**.

## 8. Analysis of Ventricular Function by Nuclear Cardiology

Radionuclide angiography and equilibrium ECG-gated cardiac blood-pool scanning have been used to assess left ventricular function in nuclear cardiology. ECG-gated myocardial perfusion SPECT with radiopharmaceuticals has recently become widely used for assessing myocardial perfusion, and dedicated analytical software has also become readily available.[330–332] This section describes the evaluation of cardiac function, focusing on this method. When ECG-gated myocardial perfusion SPECT is performed, left ventricular function is determined by using specialized software to analyze ventricular volume, EF, and regional wall motion, while diastolic function is assessed by using the differential volume curve.

The cardiac function indices calculated by ECG-gated SPECT show good reproducibility and a strong correlation with values obtained from other modalities. Information on left ventricular function and regional contractility obtained by analysis using this method adds value to myocardial perfusion data obtained from myocardial SPECT imaging, and the usefulness of such information has been recognized in patients with heart disease, especially ischemic heart disease. General methods for data collection and analysis are described here, as well as reference values for ECG-gated myocardial perfusion SPECT. A method for evaluating dyssynchrony of cardiac contraction is also described, which is based on the left ventricular phase analysis technique that has been introduced in recent years.

### 8.1 Left Ventricular Function Analysis With ECG-Gated Myocardial Perfusion SPECT

#### 8.1.1 Left Ventricular Volume and Systolic Function

ECG-gated myocardial perfusion SPECT is performed by synchronization with the R wave of the ECG for collection of SPECT data. One cardiac cycle is divided into 8–16 frames of equal duration to provide information for calculating LVEF and volume indices and for assessing regional contractility. Although ungated images are used for evaluation of myocardial perfusion, the ECG-gated SPECT data provide images for each time phase of the cardiac

**Table 22. Standard Values of Left Ventricular Volume and Ejection Fraction With ECG-Gated Myocardial Perfusion SPECT**

| | Male | | Female | |
|---|---|---|---|---|
| | Mean±SD | Range±2SD | Mean±SD | Range±2SD |
| LVEF (%) | 64±7 | 50–78 | 69±7 | 54–84 |
| EDV (mL) | 80±16 | 49–112 | 64±13 | 39–90 |
| ESV (mL) | 29±9 | 12–47 | 20±7 | 7–34 |
| EDV index (mL/m$^2$) | 47±9 | 30–64 | 42±7 | 29–55 |
| ESV index (mL/m$^2$) | 17±5 | 8–27 | 13±4 | 5–22 |

EDVI and ESVI are indices corrected by body surface area (/m$^2$). (Modified reproduction from Nakajima K[348] with permission. Copyright (2010) by the Japanese Society of Nuclear Medicine. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/).

cycle to allow assessment of wall motion. Various software programs for analysis of ventricular function are used clinically to process data obtained with ECG-gated myocardial perfusion SPECT,[333–336] and high reproducibility of the results has been shown. The LVEF and left ventricular volume calculated by ECG-gated SPECT closely correlate with data obtained by other modalities, such as cardiac MRI, echocardiography, and CT.[337–344] In general, there is no compatibility among the various software programs with regard to the absolute values obtained, and it is therefore desirable to use the same program for deciding the treatment strategies and comparison over time.[345,346] The suitable radiopharmaceuticals for performing ECG-gated SPECT are Tc-99 m-labeled tracers (i.e., Tc-99 m MIBI or tetrofosmin), which have a half-life of 6 hours and provide adequate myocardial counts at a dose of 740–1,100 MBq. When a dedicated cardiac solid-state camera with high sensitivity is used, adequate images can be obtained even with short acquisition time or reduced radiopharmaceutical dose. Many of the software programs for functional analysis were specifically developed for Tc-99 m myocardial perfusion imaging, which is commonly used in Western countries.

Reference values for Japanese patients have been determined by using data from the Working Group of the Japanese Society of Nuclear Medicine. The reference values for QGS software are shown here (**Table 22**), but these will not apply to other programs.[347,348] Tc-99 m-labeled radiopharmaceuticals for assessment of myocardial blood flow are advantageous in terms of the radiation dose and image quality, and are often used for ECG-gated SPECT. Although ECG-gated SPECT can also be performed with Tl-201- or I-123-BMIPP,[337,349,350] attention should be paid to the accuracy of contour extraction when there is a large defect (especially a severe defect on I-123 BMIPP images).

**Table 23. Standard Values of Diastolic Function With ECG-Gated Myocardial Perfusion SPECT (<60 Years Old)**

| | Mean±SD | Range±2SD |
|---|---|---|
| PFR (/s) | 2.79±0.53 | 1.73–3.85 |
| 1/3FR mean (/s) | 1.68±0.30 | 1.08–2.28 |
| TPF (ms) | 159±26 | 108–210 |
| TPF/RR interval | 0.17±0.02 | 0.13–0.22 |

(Modified reproduction from Nakajima K[348] with permission. Copyright (2010) by the Japanese Society of Nuclear Medicine. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/).

### 8.1.2 Left Ventricular Diastolic Function

The indices of left ventricular diastolic function can be calculated using data acquired with ECG-gated myocardial perfusion SPECT, by dividing the RR interval into 16–32 frames (usually 16 frames).[351–355] With nuclear medicine, diastolic function is calculated from the derivative (differential) of the volume curve (dV/dt), and the common indices are the PFR (/s), 1/3FR mean (/s), and TPF (/ms). Although these indices will vary depending on the heart rate and the curve fitting method, the reference values for the widely used QGS software (Cedars-Sinai Medical Center, USA) are shown here (**Table 23**).[347,348]

### 8.1.3 Wall Motion

Analysis of wall motion is performed by visual observation of dynamic images and assessment of 3-dimensional contours on tomographic images. With ECG-gated SPECT, the wall motion is calculated as the distance (mm) of endocardial motion between end-diastole and end-systole, and percent systolic wall thickening (%) is calculated from the percent increase in the wall count. Mapping of wall motion and systolic wall thickening is also performed, and related reference values are available.[347,356]

### 8.1.4 Changes in Cardiac Function Under Stress

ECG-gated synchronization SPECT shows high reproducibility. In patients with severe ischemia or multivessel disease, stress-induced left ventricular dysfunction may be persistent, and so-called post-stress stunning can be detected (i.e., a transient decrease in the EF and/or left ventricular dilation after stress loading). This has been reported to be a useful index for diagnostic and prognostic evaluation.[357,358] These changes are not only observed with exercise stress, but also with myocardial perfusion SPECT using coronary vasodilators such as adenosine or dipyridamole for pharmacological stress, but the underlying mechanism is not well understood. Although it has been suggested that subendocardial ischemia is involved, it should be noted that these imaging changes may not necessarily reflect actual LVEF reduction or ventricular dilation.

### 8.1.5 Phase Analysis

In nuclear cardiology, phase analysis was initiated in the 1980s. This method involves Fourier transformation of the

**Table 24. Standard Values of Phase Parameters With ECG-Gated Myocardial Perfusion SPECT Using Various Software Programs**

| | | ECTb | cREPO | QGS | HFV |
|---|---|---|---|---|---|
| 95% band width (°) | Mean±SD | 29.4±9.3 | 40.3±11.6 | 21.9±8.6 | 19.9±9.1 |
| | Range±2SD | 11–49 | 17–64 | 5–39 | 2–38 |
| Phase SD (°) | Mean±SD | 11.5±5.5 | 10.3±3.2 | 5.3±3.0 | 5.4±2.5 |
| | Range±2SD | 1–23 | 4–17 | 0–11 | 0–10 |
| Entropy (%) | Mean±SD | | 43.0±6.4 | 24.0±8.3 | |
| | Range±2SD | | 30–56 | 7–41 | |

ECTb, Emory Cardiac Toolbox with SyncTool (Emory University/Syntermed, USA); cREPO, cardioREPO (FUJIFILM Toyama Chemical); QGS, Quantitative Gated SPECT (Cedars-Sinai Medical Center, USA); HFV, Heart Function View (Nihon Medi Physics). (Reproduced from Nakajima et al 2017,[361] with permission. Copyright of authors, 2017. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/).

time–activity curve for each pixel acquired by ECG-gated cardiac blood-pool scintigraphy, followed by displaying the phase and amplitude of the trigonometric function of the fundamental wave component as a functional image. Phase analysis enables display of time phase shifts during cardiac contraction as a map, and was therefore applied to assessment of local wall motion abnormalities or detection of the accessory pathway in patients with Wolff-Parkinson-White syndrome or biventricular pacing, etc.[359] Subsequently, with the increased availability of ECG-gated myocardial perfusion SPECT, phase analysis has also been applied to analyze regional data in a similar manner using the regional time–activity curve (i.e., the curve for the change in counts during contraction and relaxation).[360] When analyzing the timing of left ventricular contraction, it is usual to create a histogram showing the distribution of phases within the left ventricle and then calculate the standard deviation, the 95% bandwidth indicating the extent of phase spread, and the level of entropy (an index of disorder or randomness). There are several advantages to performing phase analysis of ECG-gated myocardial perfusion SPECT data. First, the original image is digital and therefore can be easily quantified. Second, ECG gating is a standard acquisition method for myocardial SPECT, so additional testing is unnecessary. Third, the images generally require little manual processing, leading to high reproducibility as long as the same software is used. Fourth, regional myocardial perfusion and phase abnormalities can be directly compared on the map.

The reference values for phase analysis depend on the algorithm being used. Accordingly, the reference values for different software programs are shown in **Table 24**.[361] Interestingly, it was reported that diagnostic performance for detection of wall motion abnormalities does not vary among the software programs, even if their reference values are different,[362] and phase analysis has been used to assess the association of abnormal wall motion with induced ischemia or multivessel disease, and for differentiation between ischemic and nonischemic heart failure.[363–365] Moreover, it was reported that variation of phase values is an indicator of the efficacy of cardiac resynchronization therapy,[366–368] and is useful for prognostic evaluation,[369] although the actual usefulness of phase analysis has not yet been established.

### 8.1.6 Artifacts

Several factors have been identified as contributing to errors when functional analysis is performed with ECG-gated myocardial perfusion SPECT. When high accumulation persists in the liver or gallbladder, separation of these organs from the inferior wall of the left ventricle becomes difficult. To overcome this problem, imaging can be delayed until excretion from the liver has occurred, or in the case of accumulation in the gallbladder, an attempt can be made to wash out the accumulated tracer in the gallbladder by intake of milk or food.[370] Extraction of the left ventricular contour is possible even when there is a myocardial perfusion defect, but a significant defect occupying a wide area can lead to errors. Currently available analytical software programs tend to overestimate LVEF while underestimating volumes in patients with a small left ventricular cavity, but this issue has been addressed in some programs by modifying the algorithm.[335] Because ECG gating is used, the accuracy tends to decline when heart rate variability is large, such as when the patient has an arrhythmia during data acquisition. In addition, "noise" may affect the ECG triggers, and both the R and T waves may act as triggers in rare cases, so caution should be exercised to decide whether ECG gating is appropriate.[371]

## 8.2 Evaluation of Left and Right Ventricular Function by Cardiac Blood-Pool Scintigraphy

Cardiac blood-pool scintigraphy shows good correlation with ventriculography for evaluation of left ventricular wall motion and is useful for assessing ischemic heart disease. However, its use has been decreasing in recent years. In patients receiving cardiotoxic anticancer drugs such as doxorubicin, cardiac blood-pool scintigraphy is useful both for initial assessment of cardiac function and for follow-up.[372] Evaluation of patients receiving chemotherapy by cardiac blood-pool testing received a Class I recommendation in the ACC/AHA nuclear cardiology guidelines. Because quantification and reproducibility are both high, this test should also be considered in Japan when observation of cardiac function over time is required. In the future, evaluation is also expected to be done by 3-dimensional echocardiography and MRI, which are excellent methods for quantitative analysis.

Direct evaluation of right ventricular function by ECG-gated myocardial perfusion SPECT is impossible. Accordingly, the functional indices are calculated from images obtained in the left anterior oblique view by equilibrium ECG-gated cardiac blood-pool scintigraphy using

**Table 25. Recommendations and Levels of Evidence for Evaluation of Ventricular Function With ECG-Gated Myocardial Perfusion SPECT for the Diagnosis of Chronic Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Initial evaluation and follow-up of left ventricular function<br>Follow-up of left ventricular function in patients with coronary heart disease<br>Prognostic evaluation in patients with coronary heart disease<br>Evaluation of left ventricular function in patients with heart failure | I | B | B | IVa |
| Evaluation of left ventricular diastolic function | IIb | C | C1 | IVb |
| Evaluation of left ventricular dyssynchrony by phase analysis | IIb | C | C1 | IVb |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

**Table 26. Most Important Medications That May Affect Organ Uptake of MIBG**

| Drug | | Mechanism | Discontinuation (days) |
|---|---|---|---|
| Opioids | | Uptake inhibition | 7–14 |
| Tramadol | | Uptake inhibition | 7–14 |
| Tricyclic antidepressants | Amitriptyline, imipramine, amoxapine, others | Uptake inhibition | 7–21 |
| Sympathicomimetics | Amphetamine, ephedrine, dopamine, isoproterenol, salbutamol, others | Depletion of granules | 7–14 |
| Antihypertensive/ cardiovascular agents | Labetalol | Inhibition uptake and depletion | 21 |
| | Reserpine | Depletion and transport inhibition | 14 |
| | Guanethidine | Depletion and transport inhibition | 14 |
| | Calcium-channel blockers (nifepidine, nicardipine, amlodipine) | Increased uptake and retention | 14 |
| Antipsychotics | Phenothiazines, thioxanthenes, butyrophenones, others | Uptake inhibition | 21–28 |

(Reproduced from Flotats et al 2010,[380] with permission. Copyright, 2010, by EANM.)

Tc-99 m-labeled red blood cells. Because the left and right ventricles can be visualized simultaneously in this view, the right ventricular EF (RVEF) is calculated by setting a region of interest in the right ventricle. In recent years, a method has been developed that allows simultaneous analysis of right and left ventricular volumes and function by ECG-gated cardiac blood-pool SPECT. However, there are problems with its accuracy because the indices of right ventricular function vary depending on the setting of the valve plane, the acquisition angle, etc.[373,374] Recommendations and levels of evidence for evaluation of ventricular function with ECG-gated myocardial perfusion SPECT are shown in **Table 25**.

## 9. Myocardial Sympathetic Nervous Imaging

### 9.1 Sympathetic Innervation of the Heart

Sympathetic nerves that supply the heart originate from the bilateral stellate ganglia and form the pericardial plexus, and then are distributed with blood vessels entering the myocardium from the epicardial region.[375] The sympathetic nerve terminals produce, release, and take up neurotransmitters, and norepinephrine is found in nerve terminals distributed from the base to the apex of the heart.[376]

### 9.2 Agents for Myocardial Sympathetic Nerve Imaging

Iodine-123 MIBG is a radiopharmaceutical used for evaluation of cardiac sympathetic nerve function. Iodine-123 has a half-life of 13 hours, and the effective gamma ray energy is 159 keV. Iodine-123 MIBG has a similar structure to norepinephrine and is taken up by sympathetic nerve terminals via a similar mechanism to that for norepinephrine. Because I-123 MIBG is not metabolized by catechol-O-methyltransferase or monoamine oxidase and does not bind to catecholamine receptors, imaging with this agent reflects the kinetics of neurotransmitter uptake, storage, and release by sympathetic nerve terminals.[377–379]

Evaluation of cardiac sympathetic nerve function is also possible with PET. A variety of PET tracers are available, including C-11 hydroxyephedrine, C-11 epinephrine, and F-18 fluorodopa, but clinical use is limited and these agents are not covered by health insurance.

### 9.3 Pretreatment and Imaging

#### 9.3.1 Thyroid Block

Thyroid block is not essential because I-123 has a relatively short half-life and only emits gamma rays.[380] Administration of potassium iodide or Lugol's solution may be used to minimize exposure to the thyroid gland.

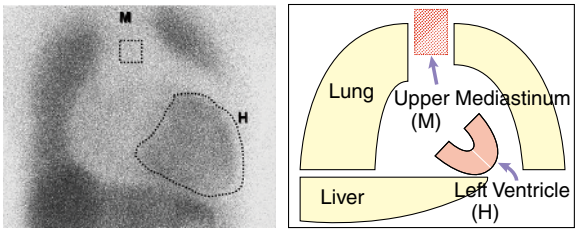



**Figure 7.** Setting of region of interest in analysis of MIBG scintigraphy. H, heart (left ventricle); M, upper mediastinum. (Reproduced from Merlet et al 1992,[385] with permission.)

### 9.3.2 Medications Before Testing

Given the diverse range of drugs that may potentially influence cardiac I-123 MIBG uptake, it is advisable to discontinue all applicable drugs before testing, including tricyclic antidepressants and antipsychotics (**Table 26**).[380]

### 9.3.3 Imaging Technique

A dose of 111 MBq of I-123 MIBG is injected intravenously under resting conditions. Imaging should be performed twice; that is, 15–30 min (early images) and 180–240 min (late images) after intravenous injection. Both planar and SPECT images are collected. Attention must be paid to the collimator used during imaging. Because measured values vary between low-energy collimators and medium-energy collimators, correction with a conversion factor is necessary according to the type of collimator.[381,382]

### 9.3.4 Evaluation Method

The heart-to-mediastinum ratio (H/M ratio) and the washout rate are calculated from planar images, and regional assessment is performed using SPECT images. The H/M ratio and washout rate are calculated by setting regions of interest on the entire heart and the upper mediastinum in a planar image (**Figure 7**).[383] Formulae for calculating the H/M ratio and washout rate are as follows:

H/M ratio = cardiac count/mediastinal count*

Washout rate (%) = {(cardiac count [early image] − mediastinal count [early image]) − (cardiac count [late image] − mediastinal count [late image])} / (cardiac count [early image] − mediastinal count [early image]) × 100

*Cardiac/mediastinal count ratio is based on an average count for a unit area of the region of interest.

The reference value for the H/M ratio is 2.2–4.0 on early images and 2.2–4.4 on late images when a standard medium-energy collimator is used.[381,382] The reference value for the washout rate is 6–30% with correction for physiological decay of I-123.

## 9.4 Clinical Significance

The most important indication for I-123 MIBG imaging is assessing the prognosis of patients with heart diseases, and it is useful for risk stratification in patients with heart failure, cardiomyopathy, or ventricular tachyarrhythmias.

Myocardial sympathetic nerve function is impaired in patients with coronary heart disease, and I-123 MIBG accumulation is decreased in regions affected by ischemia or scarring.[384–388] Myocardial perfusion scintigraphy is more useful for diagnosis of coronary heart disease, and evaluation of sympathetic nerve dysfunction is only complementary to anatomical assessment of coronary artery pathology. On the other hand, I-123 MIBG imaging is considered to be useful for risk stratification in patients who have chronic coronary heart disease with heart failure (ischemic heart failure) or coronary heart disease associated with ventricular tachyarrhythmias. Such uses are described below.

### 9.4.1 Prognostic Evaluation (Table 27)

The H/M ratio and washout rate have been shown to be significant prognostic factors in patients with heart failure, including those with coronary heart disease. According to studies from Japan, both the late H/M ratio and the washout rate were predictors of cardiac events in patients with heart failure and cardiac dysfunction, including patients who had coronary heart disease.[389,390] An overseas study also showed that the late-phase H/M ratio was a predictor of cardiac events,[391] and adding the H/M ratio to models predicting cardiac events improved their accuracy.[392] In those reports, the cutoff value for the H/M ratio was 2.0 when converted to the ratio for a standard medium-energy collimator. Moreover, it has been reported that appropriate ICD therapy for ventricular tachyarrhythmias is frequent when local accumulation of I-123 MIBG is substantially decreased in the late phase, and this finding may be useful for predicting lethal arrhythmias.[393]

### 9.4.2 Diagnosis

Cardiac sympathetic nerve imaging has a limited role in the diagnosis of chronic coronary heart disease, and evaluating cardiac sympathetic nerve function alone is not sufficient for assessment of heart disease. Instead, assessment should be performed by integrating data from various modalities, including morphological evaluation by coronary angiography or coronary CT, detection of ischemia by methods such as stress myocardial perfusion scintigraphy, and the assessment of myocardial viability by using $^{18}$F-FDG-PET and LGE MRI.

Accumulation of I-123 MIBG is reduced in myocardial regions affected by infarction or ischemia. In patients with

**Table 27. Recommendations and Levels of Evidence for Prognostic Evaluation by Myocardial Sympathetic Nervous Imaging for Heart Failure Due to Chronic Coronary Heart Disease (Ischemic Heart Failure)**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Prognostic evaluation for ischemic heart failure | IIa | C | B | IVb |

Among the studies for heart failure, the proportion of chronic coronary heart disease in study subjects varied depending on the report. COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

**Table 28. Summary of Myocardial Sympathetic Nervous Imaging**

| | | | |
|---|---|---|---|
| **I-123 MIBG** | Application | Evaluation of cardiac sympathetic nervous function | |
| | Characteristics | Half-life | 13 hours |
| | | Effective gamma ray energy | 159 keV |
| | | Structure | Similar to norepinephrine |
| **Pretreatment and imaging** | Pretreatment | Thyroid block | Not essential |
| | | Discontinuation | Tricyclic antidepressants, antipsychotics |
| | Imaging technique | Dose | 111 MBq |
| | | Imaging | Early: 15–30 min after intravenous infection |
| | | | Late: 180–240 min after intravenous injection |
| | | | Planar and SPET images |
| **Evaluation method** | Heart-to-mediastinum ratio (H/M ratio) | Cardiac count/mediastinal count | |
| | Washout rate (%) (WR) | $\frac{\text{(Cardiac count [early image]} - \text{mediastinal count [early image])} - \text{(Cardiac count [late image]} - \text{mediastinal count [late image])}}{\text{Cardiac count [early image]} - \text{mediastinal count [early image]}} \times 100$ | |
| | Reference value | H/M ratio: 2.2–4.4 | |
| | | WR: 6–30% (with correction for physiological decay of I-123) | |
| **Clinical significance** | Prognostic evaluation | Heart failure, ventricular tachyarrhythmias | |
| | Diagnosis | Limited role in the diagnosis of chronic coronary heart disease | |
| | Evaluation of treatment effect | Pharmacotherapy, cardiac resynchronization therapy | |

myocardial infarction and angina pectoris, the MIBG defect is often more extensive than the zone of decreased blood flow, and areas of mismatch with blood flow may reflect myocardium at risk.[384–388] Previous reports have shown that I-123 MIBG has the same performance for diagnosis of coronary heart disease as exercise Tl-201 scintigraphy.[394] However, accumulation in the inferior wall of the left ventricle decreases with age, leading to an increase in false-positive results, and evaluation of the inferior wall is often difficult due to artifacts.[395,396] Therefore, it should be noted that regional accumulation in the inferior wall may be reduced in the absence of coronary heart disease.[397]

### 9.4.3 Evaluation of Treatment Effect

Imaging with I-123 MIBG can be used to judge the effect of treatment for heart failure as a complication of chronic coronary heart disease. Iodine-123 MIBG imaging was reported to be useful when assessing the efficacy of standard pharmacotherapy (angiotensin-converting enzyme inhibitors, $\beta$-blockers, aldosterone receptor antagonists, etc.) for heart failure.[398–402] It was also reported to be helpful for evaluating the effect of cardiac resynchronization therapy.[403,404] Summary of myocardial sympathetic nervous imaging are shown in **Table 28**.

## 10. Myocardial Fatty Acid Imaging

### 10.1 Myocardial Energy Metabolism

The heart constantly requires an abundant source of energy (ATP) to function. Under aerobic conditions, more than 60% of the myocardial energy requirement is obtained from long-chain fatty acids,[405,406] with the remainder being mainly derived from glucose and only a few percent from amino acids and lactic acid (fatty acid–glucose cycle). However, $\beta$-oxidation of fatty acids requires an abundant supply of oxygen and is easily affected by impaired myocardial blood flow (ischemia).[407,408] This makes it possible to sensitively detect ischemic injury by assessing myocardial fatty acid metabolism. PET can be used to evaluate fatty acid metabolism by assessing the $\beta$-oxidation of C-11-labeled palmitic acid (which is used in vivo). However, metabolism of this straight-chain fatty acid is rapid and it is thus difficult to obtain good images and unsuitable for clinical use. On the other hand, iodine (I)-123 BMIPP and I-123-iodophenyl-9-methyl-pentadecanoic acid (I-123-9-MPA) are long-chain fatty acids with side chains in which a methyl group has been introduced at the position of palmitic acid.

These agents are not susceptible to $\beta$-oxidation, show good myocardial retention, and can be easily detected with a conventional gamma camera, allowing this imaging method to capture energy metabolism and fatty acid metabolism by cardiomyocytes at the molecular level in daily clinical practice. This method does not directly assess $\beta$-oxidation, but reflects the uptake of long-chain fatty acids by cardiomyocytes via specific transporters, as well as their intracellular transport and storage (triglyceride pool). Because accumulation of I-123 BMIPP or I-123-9-MPA depends on the myocardial ATP concentration,[409,410] it indirectly reflects myocardial fatty acid metabolism. This section describes myocardial I-123 BMIPP imaging, which is widely used in routine practice and for which relevant clinical data have been obtained.

### 10.2 Myocardial I-123 BMIPP Imaging

#### 10.2.1 Data Collection

A low blood glucose level is preferable to increase the uptake of fatty acids by the myocardium. Therefore, 111–148 MBq of I-123 BMIPP (3–4 mCi) is administered intra-

**Table 29. Correlations Between Myocardial Blood Flow (MBF) and Metabolism of Glucose and Long-Chain Fatty Acids (LCFA) in Normal Myocardium and in Various Pathophysiologies of Myocardial Ischemia**

| | MBF at rest (myocardial viability) | MBF at stress | Regional wall motion at rest | Myocardial energy metabolism in the fasting condition | |
|---|---|---|---|---|---|
| | | | | BMIPP (LCFA) accumulation | FDG (glucose) accumulation |
| Normal myocardium | Normal | Increased | Normal | Normal | No (physiological uptake) |
| Ischemic myocardium (reversible ischemia) | Normal | Insufficient increase (ischemia) | Normal (reversible decrease under stress) | Normal to decreased (reversible) | Increased (compensatory) |
| Stunned myocardium (Alleviation of acute ischemia) | Normal to mild decrease | Increased | Decreased (reversible) | Decreased (reversible) | Increased (compensatory) |
| Hibernating myocardium (persistent ischemia) and Ischemia-induced failing myocardium | Mild-to-moderate decrease | Insufficient increase (ischemia) | Decreased (reversible) | Decreased (reversible) | Increased (compensatory) |
| Infarcted myocardium | Severe decrease | Severe decrease | Severe decrease (irreversible) | Severe decrease (irreversible) | Severe decrease (irreversible) |

venously at rest in the fasting state on the day of the test. A frontal plane image is obtained 20–30 min later (this may be omitted), followed by acquisition of tomographic images (SPECT). With l-123 BMIPP imaging, simultaneous acquisition of data on another radionuclide (such as TI-201 for assessing myocardial blood flow) is possible because of the differences in the energy peak. This allows accurate comparison of myocardial blood flow and fatty acid metabolism in the same tomographic image. Although interference occurs during simultaneous acquisition of data on 2 radionuclides (primarily down-scatter by I-123 has an effect on Tl-201 images), the effect is smaller when accumulation of I-123 BMIPP is abnormal. Therefore, it becomes easier to accurately evaluate metabolic dysfunction in ischemic myocardium and to identify the presence/absence of myocardial flow-fatty acid metabolism mismatch (described later). However, simultaneous acquisition of data on 2 radionuclides by using I-123 BMIPP and Tc-99 m for myocardial blood flow imaging is difficult with a conventional gamma camera because the energy peaks are too close, and a high-resolution semiconductor camera is required.

### 10.2.2 Analysis (Visual and Semiquantitative Evaluation)

Visual assessment of SPECT images (evaluation of the site, extent, and severity of decreased accumulation) and semiquantitative visual evaluation are generally performed in a similar manner to the evaluation of myocardial perfusion SPECT imaging, based on 17 segments and a 5-point score. A 2-dimensional polar coordinate display method using concentrically arranged short-axis tomographic images is also widely used because it facilitates evaluation of abnormal accumulation and enables quantitative assessment. Recent advances in image analysis software have made it easier to automate the scoring of the 17 segments and to quantify abnormal accumulation on the 2D polar coordinate display. Such software has also been applied for prognostic evaluation and for quantitation of blood flow–metabolism mismatch.[411,412]

When the result is normal, myocardial distribution of I-123 BMIPP is uniform because of good accumulation of this agent. I-123 shows less attenuation than Tl-201 because of its higher energy, and there is a smaller decrease in accumulation in the inferior wall (artifact) due to absorption by the diaphragm with I-123 than with TI-201.[413] Myocardial I-123 BMIPP imaging with an early (20–30 min after administration) and late (3–4 hours after administration) imaging protocol has been reported, as well as methods for evaluating the myocardial washout rate. However, the clinical significance of these methods has not been established in patients with coronary heart disease.

## 10.3 Mechanism and Clinical Significance of Abnormal Myocardial I-123 BMIPP Accumulation

As described above, abnormally reduced myocardial I-123 BMIPP accumulation theoretically reflects one or more of the following abnormalities: decreased uptake of long-chain fatty acids by a specific transporter (CD36) in the cardiomyocyte membrane, abnormal handling of long-chain fatty acids by a specific intracellular transporter (H-FABP) in cardiomyocytes, decreased myocardial lipid storage (triglyceride pool), impaired mitochondrial transport (carnitine shuttle), and decreased mitochondrial $\beta$-oxidation with a resultant decrease in the myocardial ATP concentration.

The most important factor in impaired myocardial fatty acid metabolism is reduced myocardial blood flow that causes myocardial ischemia. When myocardial ischemia occurs and leads to oxygen deficiency, $\beta$-oxidation of fatty acids in the mitochondria (which requires abundant oxygen) is rapidly inhibited and ATP production is reduced. Because ATP depletion means that fatty acids are not activated to form acyl-CoA in cardiomyocytes (decreased fatty acid consumption), the myocardial fatty acid storage pool shrinks and fatty acid transport to the mitochondria is inhibited. These ischemic derangements of myocardial fatty acid metabolism result in abnormal myocardial accumulation of I-123 BMIPP. Abnormal myocardial fatty acid metabolism often persists after restoration of coronary blood flow and alleviation of myocardial ischemia by acute coronary revascularization, and this phenomenon is known as ischemic memory.[414–416] The existence of ischemic memory greatly improves the accuracy of detecting myocardial ischemia by I-123 BMIPP imaging, and ischemic memory occurs because recovery of myocardial fatty

acid $\beta$-oxidation is delayed, unlike recovery of glucose metabolism (**Table 29**).

During this delay period, ATP production by glucose metabolism is insufficient to maintain myocardial viability and it takes time to normalize cardiomyocyte function (contractility). Based on ischemic memory, hibernating myocardium and stunned myocardium caused by myocardial ischemia can be detected by myocardial I-123 BMIPP imaging. **Table 29** summarizes the relationships among myocardial blood flow, contractility (wall motion), myocardial fatty acid metabolism (I-123 BMIPP accumulation), and myocardial glucose metabolism ($^{18}$F-FDG accumulation) in healthy myocardium, ischemic myocardium, myocardium after alleviation of acute ischemia (stunned myocardium), chronically ischemic myocardium (hibernating myocardium), and infarcted (necrotic) myocardium. By comparing myocardial blood flow, contractility (wall motion), and myocardial fatty acid metabolism, the detailed pathophysiology of ischemic myocardial injury can be understood, helping to determine the effect of treatment and assess the prognosis. This imaging technique is safe and can be performed with a conventional gamma camera. It is a noninvasive resting examination with no effect on hepatorenal or cardiac function, and is unaffected by the presence of comorbidities. Unlike $^{18}$F-FDG imaging, BMIPP imaging is also able to diagnose coronary heart disease in patients with diabetes or hyperlipidemia, as in nondiabetic patients, because there is only limited influence of substrates in the blood (glucose, cholesterol, fatty acids, insulin, etc.).[417,418]

## 10.4 Suspected or Confirmed Stable Chronic Coronary Heart Disease

The effect of ischemia on myocardial fatty acid metabolism depends on the severity of the myocardial ischemia. Hence, the diagnostic accuracy of myocardial I-123 BMIPP imaging is higher for acute and severe ischemia and lower for chronic and mild ischemia. In patients with stable chronic coronary heart disease, myocardial ischemia is induced by exercise or other stresses, and can be persistent, often being painless and occult. Moreover, recovery of myocardial fatty acid metabolism is delayed after alleviation of ischemia (improvement of myocardial blood flow). Accordingly, myocardial I-123 BMIPP imaging at rest can detect ischemia, determine its severity, and investigate the presence or absence of recent ischemic episodes, and detection of ischemic memory is of diagnostic significance in patients with stable chronic coronary heart disease.[419–421]

### 10.4.1 Diagnostic Significance

A major advantage of myocardial I-123 BMIPP imaging is that it is a resting examination. Therefore, it is useful when it is difficult for the patient to perform exercise or pharmacological stress testing (e.g., contraindications to drugs [bronchial asthma, atrioventricular block, severe bradycardia, hypotension, etc.], use of antianginal drugs such as nitrates and $\beta$-blockers, and suspected coronary heart disease when ACS cannot be excluded). The presence of a certain level of chronic myocardial ischemia is required for the onset of myocardial fatty acid metabolism disorder. It has been reported that the diagnostic accuracy of I-123 BMIPP imaging for stable chronic coronary heart disease is almost equivalent (concordance of ≈90%) to that of stress myocardial perfusion imaging, which has already been established as useful.[421] Although the diagnostic accuracy for reversible ischemia in routine clinical practice is not necessarily high (50–60%), it is relatively consistent with resting wall motion abnormalities (70%).[422] Thus, the diagnostic accuracy of I-123 BMIPP imaging is clearly superior to that of resting myocardial perfusion imaging.[419,420,422–424]

In the absence of a history of myocardial infarction, abnormal BMIPP accumulation may be seen despite normal myocardial perfusion (i.e., mismatch occurs between myocardial blood flow and BMIPP accumulation). When stress myocardial perfusion imaging is negative (false-negative result, multivessel disease, heart failure, insufficient loading, etc.), if decreased myocardial BMIPP accumulation is consistent with a coronary artery territory, the possibility of coronary heart disease and a prior ischemic episode is high. Thus, multiple sites of abnormal BMIPP accumulation suggest the possibility of multivessel disease.[417,424,425]

### 10.4.2 Vasospastic Angina

Vasospastic angina may be induced by exercise, exposure to cold, or other stress, and is often associated with stable or chronic coronary heart disease. Conventional stress testing with exercise loading or vasodilators does not have a high diagnostic accuracy for vasospastic angina. In addition, it is not easy to detect spontaneous attacks leading to myocardial ischemia, because severe attacks often occur at night or in the early morning. However, this disease can give rise to severe ischemia associated with ST elevation that persists for a relatively long time, which means myocardial I-123 BMIPP imaging can be used to diagnose coronary vasospasm with a high sensitivity and specificity (both 70–90%), even after the offset of vasospasm, and is also useful for determining the effect of treatment with calcium antagonists or other agents.[426–429] When a test result is abnormal, coronary angiography or coronary CT is subsequently required to assess coronary artery morphology. Because abnormal myocardial fatty acid metabolism is a reflection of ischemia, the diagnostic accuracy of this test is influenced by the severity of ischemia and the time until recovery from ischemia, so caution should be exercised regarding negative results.

### 10.4.3 Hibernating Myocardium

Hibernating myocardium is affected by chronic, persistent ischemia and is associated with abnormal regional wall motion. In this condition, myocardial contractility is suppressed (hibernation) because of severe persistent ischemia, even in the absence of myocardial necrosis, and its diagnosis is important for determining the indications for procedures such as coronary revascularization. If myocardium is hibernating, its viability is maintained and contractility can be restored within several months after alleviation of chronic myocardial ischemia. However, whether or not hibernating myocardium affected by chronic ischemia is actually viable usually cannot be judged from assessment of regional wall motion alone, although judgment is possible if reversible myocardial ischemia is induced. In contrast to necrotic myocardium, hibernating myocardium appears almost normal on resting myocardial imaging (indicating its viability), while showing impaired fatty acid metabolism and increased glucose metabolism,[417] as well as reduced accumulation of I-123 BMIPP (indicating ischemic injury). Therefore, mismatch between these findings can be diagnosed by imaging at rest. The severity and extent of abnormal myocardial I-123 BMIPP accumulation

correlate with the decrease in wall motion and LVEF. Because wall motion and LVEF show improvement within several months after coronary revascularization, I-123 BMIPP imaging is useful for both diagnosing hibernating myocardium and predicting its recovery.[420,430–433]

### 10.4.4 Prognostic Evaluation

Because abnormal myocardial I-123 BMIPP accumulation also reflects prior ischemic events, chronic persistent abnormal accumulation is related to prognosis.[434–438] In patients with coronary heart disease, including those with ACS or chest pain, the severity of reversible abnormal myocardial blood flow, a low LVEF, and diabetes mellitus are conventionally considered to be significant prognostic indicators. The severity of abnormal myocardial I-123 BMIPP accumulation and mismatch of I-123 BMIPP accumulation with blood flow are also significantly associated with future cardiac events, and these indicators can contribute to more accurate prediction of the prognosis.[438] In patients without myocardial infarction, the prognosis is good if myocardial I-123 BMIPP imaging is normal or slightly abnormal (i.e., this test has a high negative predictive value).[439] Thus, risk stratification (differentiation between low- and high-risk patients) and prognostic evaluation can be performed for coronary heart disease by using myocardial I-123 BMIPP imaging, based on the fact that inhibition of myocardial fatty acid metabolism is a sensitive response to myocardial ischemia and reflects both infarcted myocardium and ischemic myocardium at risk of further damage in future cardiac events.

### 10.4.5 Ischemic Heart Failure and Ischemic Cardiomyopathy

Patients with chronic coronary heart disease, especially those with heart failure, are increasing in number, although they may not have typical symptoms of stable chronic coronary heart disease. Caution should be especially exercised with regard to elderly patients and those with diabetes or renal failure. If obvious organic disease (hypertensive cardiac hypertrophy, valvular disease, congenital heart disease, cardiomyopathy, etc.) is ruled out, then it is important to identify heart failure caused by coronary heart disease (ischemic heart failure and ischemic cardiomyopathy). Coronary angiography is required for a definitive diagnosis, but it is often not easy to perform because of the poor general condition of the patient, including renal dysfunction. In such patients, myocardial I-123 BMIPP imaging is a relatively easy and safe resting test. A defect of I-123 BMIPP accumulation corresponding to a specific coronary artery territory is strongly suggestive of coronary heart disease.

Simultaneously performing myocardial perfusion imaging (i.e., simultaneous imaging with 2 radionuclides) can distinguish between heart failure due to left ventricular remodeling after myocardial infarction, in which myocardial viability cannot be expected (defect of I-123 BMIPP accumulation and myocardial perfusion defect at rest), and heart failure due to coronary heart disease where revascularization is expected to be effective. In the latter case, I-123 BMIPP accumulation is abnormal even though resting myocardial perfusion is maintained to some extent, indicating viable myocardium (myocardial blood flow–metabolism mismatch).[440] In patients with idiopathic dilated cardiomyopathy, which is often difficult to differentiate from ischemic cardiomyopathy, it is known that cardiomyocyte injury, subendocardial ischemia, and impaired myocardial energy production can lead to decreased BMIPP accumulation and impaired blood flow related to fibrosis, and abnormal I-123 BMIPP accumulation is associated with the prognosis.[441,442] Unlike patients with ischemic heart failure, these patients have multiple mild, diffuse, or heterogeneous abnormalities that are not consistent with any coronary artery territory, and mismatch between blood flow and BMIPP accumulation is also mild. These points allow idiopathic cardiomyopathy to be distinguished from ischemic heart failure.

**Table 30. Recommendations and Levels of Evidence for Myocardial BMIPP Imaging in Various Pathophysiologies of Myocardial Ischemia for the Diagnosis of Chronic Coronary Heart Disease**

| Diagnostic target | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Myocardial ischemia | IIa | C | B | IVa |
| Hibernating myocardium | IIb | C | B | IVb |
| Vasospastic angina | IIa | C | B | IVa |
| Myocardial ischemia in dialysis patients | I | B | B | III |
| Risk & prognosis assessment in dialysis patients | I | B | B | III |
| Risk & prognosis assessment | IIa | B | B | IVa |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

### 10.4.6 Diagnosis and Prognostic Evaluation in Patients With Diabetes or CKD and Dialysis Patients

Patients with diabetes or CKD, as well as patients on dialysis, often have concomitant hypertension and a high risk of coronary heart disease leading to cardiovascular events such as heart failure and sudden death. However, diagnosis tends to be delayed because of a lack of symptoms and difficulty in performing tests for coronary heart disease using contrast medium. Combined with the influence of contrast-induced renal damage, delayed diagnosis worsens the prognosis of such patients. Although stress myocardial perfusion imaging is generally useful in these high-risk patients, myocardial I-123 BMIPP imaging can be an alternative when performing a stress test is difficult because of the patient's general condition and blood pressure. Several investigations, including a multicenter Japanese study (B-SAFE study), have identified the usefulness of I-123 BMIPP imaging for diagnosis of asymptomatic coronary heart disease in patients with diabetes or renal dysfunction,[443,444] as well as for predicting cardiovascular events and the prognosis,[445–449] evaluation of treatment,[450] and assessing the risk of sudden death in patients on chronic dialysis[451] (**Table 30**).

## 11. Positron Emission Tomography (PET)

### 11.1 Significance in the Diagnosis of Chronic Coronary Heart Disease

When a pair of high-energy gamma rays (511 keV) are

**Table 31. Recommendations and Levels of Evidence for Assessment of Myocardial Viability Using FDG-PET for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Evaluation of CAD patients with left ventricular dysfunction | IIa | B | B | III |
| Diagnosis of IHD in patients with left ventricular dysfunction in conjunction use with myocardial perfusion imaging | IIa | C | B | IVb |

CAD, coronary artery disease; COR, class of recommendation; GOR, grade of recommendation; IHD, ischemic heart disease; LOE, level of evidence.

emitted at 180 degrees from opposite directions as a result of the annihilation of positron-emitting radionuclides, paired and opposed detectors obtain positional information by localizing their source along a straight line of coincidence. With these emission mechanisms and scan techniques, PET has a greater sensitivity of gamma ray count per unit time and higher spatial resolution than SPECT, and CT attenuation correction is generally performed and has achieved better image quality as hybrid PET/CT scanners become popular.

A cardiovascular PET scan for diagnosis of myocardial viability using $^{18}$F-FDG has only been covered by health insurance since 2002. Since 2012 it can be used for diagnosis of inflammation in cardiac sarcoidosis using FDG and evaluation of myocardial perfusion using $^{13}$N-ammonia, and since 2018 for diagnosis of large vessel vasculitis using FDG. $^{18}$F-FDG has a relatively long half-life of about 110 min and can be supplied by on-site preparation using a small cyclotron or purchased from manufacturers. In contrast, $^{13}$N-ammonia used for myocardial perfusion PET has a short half-life of 10 min and on-site preparation is required.

### 11.1.1 Assessment of Myocardial Viability Using $^{18}$F-FDG (Table 31)

$^{18}$F-FDG is a glucose analog in which the hydroxyl group at the C-2 position of glucose is substituted by F-18. Like glucose, $^{18}$F-FDG is taken up into cells via a glucose transporter in the plasma membrane and phosphorylated by hexokinase. Unlike glucose, $^{18}$F-FDG is retained in the cell without being metabolized.[452] Because of high uptake by cells with active glucose metabolism, $^{18}$F-FDG imaging is mainly used for the diagnosis of malignant tumors. However, cardiomyocytes also show substantial accumulation of $^{18}$F-FDG.[453,454] In Japan, diagnosis of myocardial viability by $^{18}$F-FDG imaging in patients with poor left ventricular function is covered by health insurance.

In patients with OMI ventricular dysfunction and stenosis of the coronary artery supplying the infarcted region, viable myocardium is assumed to be present in this region if the wall motion and LVEF are improved by recanalization (reperfusion) therapy.[232,455] By determining whether viable myocardium exists in the infarct zone before recanalization (reperfusion) therapy, its effect can be predicted and unnecessary invasive treatment can be avoided.[309] In patients with residual viable myocardium, the incidence of cardiac events is lower after recanalization (reperfusion) therapy than after conservative treatment with drugs.[229,306,456] Determination of myocardial viability using FDG-PET in patients with heart failure due to coronary heart disease is only covered by health insurance if it is difficult to judge using myocardial perfusion SPECT. That is, patients with poor left ventricular function who are judged to have no viable myocardium are only eligible for FDG-PET imaging. In actual practice, evaluation of myocardial viability by FDG-PET is often performed in patients without viable myocardium on perfusion imaging who show insufficient improvement of left ventricular function with medication, presumably in anticipation of a therapeutic effect of recanalization (reperfusion) therapy.

The myocardium primarily obtains energy from aerobic metabolism of fatty acids and anaerobic glycolysis via the TCA cycle. However, energy can also be supplied by a variety of other substrates, such as lactate, ketone bodies, and amino acids, and the source is determined by a range of factors, including food intake, hunger, exercise, myocardial ischemia, and cardiac dysfunction.[457] Tests for diagnosis of myocardial viability are performed in the presence of high glucose uptake in order to promote uptake of $^{18}$F-FDG by viable cardiomyocytes. If the patient does not have diabetes, he/she fasts for 6 hours or longer and then orally ingests 50–100 g of glucose at 30 min before $^{18}$F-FDG administration. In patients with diabetes mellitus, continuous intravenous infusion of insulin and glucose is performed to maintain a constant glucose level (glucose–insulin clamp)[458] or oral glucose loading is followed by administration of 1–5 units of rapid-acting insulin, depending on the blood glucose level.[459]

$^{18}$F-FDG is administered at a dose of 185–444 MBq (3–7 MBq/kg), depending on the scanner specifications, but by using 3-dimensional acquisition, which has higher count sensitivity than 2-dimensional acquisition, the $^{18}$F-FDG dose can be reduced to 111–259 MBq (2–5 MBq/kg).[460] From at least 45 min after $^{18}$F-FDG administration (usually 60–90 min), a 1-bed scan for cardiac imaging is carried out. The longer the interval from administration, the better contrast of myocardium-to-the-background is achieved as $^{18}$F-FDG uptake in the blood pool decreases. Although the contrast is better at ≥90 min after $^{18}$F-FDG administration, the count activity decreases.

Reconstructed images of the left ventricular myocardium are obtained in 3 views (short-axis, vertical long-axis, and horizontal long-axis), and interpretation is usually performed by comparison with myocardial perfusion SPECT or PET imaging. With myocardial perfusion SPECT images at rest, myocardial viability is considered if myocardial uptake in the infarct area is ≥50% (for Tl) or ≥60% (for Tc) in comparison with normal area. With FDG-PET alone, the presence of viable myocardium can be assumed if ≥50% uptake is seen in the infarct area.[461] Myocardial viability is also considered in the infarct area if $^{18}$F-FDG uptake is greater than that observed by resting perfusion imaging.

**Table 32. Recommendations and Levels of Evidence for Ammonia Myocardial Perfusion PET**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Diagnosis of CAD in patients with intermediate to high pretest probability | I | B | A | IVa |
| Risk stratification and prognostic analysis based on ischemic and infarct volume | I | B | A | IVa |
| Risk stratification and prognostic analysis using quantitative myocardial perfusion kinetic analysis in conjunction with visual analysis | I | B | A | IVa |
| Risk stratification and prognostic analysis using ECG-gated left ventricular function analysis in addition to visual analysis | IIa | B | B | IVa |
| Detection of left main disease or severe multivessel disease by quantitative myocardial perfusion kinetic analysis | IIa | C | B | IVb |

CAD, coronary artery disease; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

Even if perfusion imaging shows myocardial uptake ≤50% in the infarct area, greater $^{18}$F-FDG uptake indicates myocardial viability.[302,462] A meta-analysis showed that FDG-PET has sensitivity of 91% and specificity of 61% for diagnosis of myocardial viability, with its sensitivity being higher than that of myocardial perfusion imaging or dobutamine stress echocardiography.[232] Therefore, FDG-PET is unlikely to underestimate residual viable myocardium compared with other modalities, but consideration should be given to revascularization not always achieving improvement of left ventricular function even when viability is expected from the FDG-PET results. It has also been reported that FDG-PET can distinguish between ischemic and nonischemic cardiac dysfunction with a sensitivity of 100% and specificity of 80%.[463]

### 11.1.2 Evaluation of Myocardial Blood Flow Using $^{13}$N-Ammonia (Table 32)

Myocardial perfusion PET using $^{13}$N-ammonia has been covered by health insurance since April 2012, but is only applicable when ischemic heart disease is difficult to diagnose with other modalities. Tracers used for myocardial perfusion PET include rubidium (Rb)-82, which has a physical half-life of 76s, O-15 water (2 min), and ammonia N-13 (10 min). In Japan, only $^{13}$N-ammonia is covered by health insurance. $^{13}$N-Ammonia accumulates in the myocardium after conjugation with glutamate, has a relatively long half-life among perfusion PET tracers, and has a short positron range, enabling the collection of high-quality images suitable for visual analysis.[464] The first-pass myocardial extraction rate is also high (≈80%).[465] so it is suitable for quantitative analysis of myocardial blood flow.

Quantification of myocardial blood flow using compartment model kinetic analysis in addition to visual assessment has currently become a standard procedure. Usually, 370–740 MBq of $^{13}$N-ammonia is administered from the right cubital vein followed by more than 30 mL of saline by bolus injection in ≤30 s. List-mode acquisition is performed at the same time or shortly before injection of the tracer to obtain dynamic data for the kinetic analysis. Pharmacological stress such as adenosine or cold stimulation is generally performed for stress imaging. The procedure of pharmacological stress is the same as for SPECT. If the scan interval between rest and stress imaging is set at around 40–50 min (4–5-fold the half-life of $^{13}$N-ammonia), residual tracer from the earlier session can be ignored and both imaging sessions can be performed at the same injection dose, regardless of the order of rest and stress imaging.

For visual analysis, image reconstruction is performed using 5–15 min of data collected between 90 s and 3 min after administration, because most of the tracer is taken up into the myocardium by 90 s after administration. A study comparing several software programs for quantitative analysis of myocardial blood flow found high reproducibility of quantitative analysis, with little difference between different software programs.[466]

A meta-analysis demonstrated good diagnostic performance of myocardial perfusion PET by visual assessment for coronary stenosis detected by invasive coronary angiography as the gold standard, with sensitivity of 90–93% and specificity 81–88%, which were superior to those of SPECT.[258,467,468] It has been reported that normal PET results promise low probability of coronary stenosis and extremely low incidence of cardiac events with its high negative predictive value.[469] Reports also indicate that the severity of ischemia or infarction by semiquantitative visual analysis of myocardial perfusion PET correlates with the prognosis.[470–473] LVEF obtained by ECG-gated analysis has been reported as an independent prognostic factor.[474,475] The CFR obtained by quantitative PET analysis is a prognostic indicator independent of a visual assessment, and a combination of these 2 parameters allows accurate prognostic risk stratification.[476,477] In the daily clinical setting, myocardial perfusion PET is useful for patients with multivessel disease in whom diagnosis of ischemia by myocardial perfusion SPECT is difficult and often underestimated, especially those with left main trunk disease and triple-vessel disease.[477–479] Rb-82, which is easily generated by generators and covered by health insurance in the USA, has been used in most of the reported evidence about myocardial perfusion PET, but the number of reports on $^{13}$N-ammonia N-13 is increasing.

Myocardial perfusion PET is associated with less radiation exposure than SPECT and shows better diagnostic performance. However, $^{13}$N-ammonia requires on-site preparation using a small cyclotron, so it can only be performed at a limited number of centers at present. Myocardial perfusion PET could be performed at many centers with PET scanners if a perfusion tracer with F-18, which has a long half-life and can be delivered by manufacturers, is approved for use in Japan in the future. For example, $^{18}$F-flurpiridaz has potential for future use, a

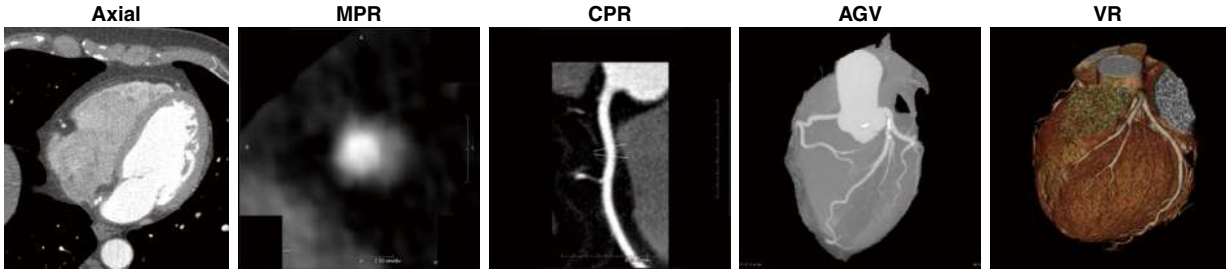



**Figure 8.** Various image reconstruction formats in cardiac CT. AGV, angiographic view; Axial, axial image; CPR, curved planar reformat; MPR, multiplanar reformat; VR: volume rendering.

high myocardial extraction ratio of 94%,[480] and is rapidly taken up from the blood by cardiomyocytes, showing good retention. Compared with ammonia, $^{18}$F-flurpiridaz achieves higher myocardial contrast vs. the blood pool, lungs, and liver, which is more suitable for visual assessment,[481] and it is also excellent for quantitative analysis of blood flow.[482]

## 12. Coronary CT Angiography (CCTA)

The use of CCTA, a technique of cardiac CT, has been rapidly and widely spreading in cardiovascular medicine. To maximize the usefulness of cardiac CT, this section will first provide the basics of cardiac CT, including its characteristics, principles of data acquisition, and management of radiation exposure. Next, it will also outline the evaluation and reporting systems used in the assessment of CCTA and cardiac CT. Finally, this section will highlight the utilization of both the morphological coronary artery assessment (stenosis and plaque) and newly developed functional assessment (myocardial perfusion and coronary blood flow) assessments through cardiac CT in the diagnostic algorithm for chronic coronary heart disease.

Given the technical progress in MDCT, CCTA has rapidly become a reliable diagnostic tool for CAD in clinical practice.[483] In fact, invasive coronary angiography has long been considered the standard diagnostic technique, whereas CCTA represents an increasingly important tool for noninvasive imaging and assessment of ischemic heart disease. It is comparable to other techniques such as stress ECG, stress myocardial perfusion imaging (SPECT, MRI, and PET) and stress echocardiography.[2] In addition to morphological assessment of coronary artery stenosis and plaque (**Figure 8**) by CCTA, cardiac CT enables functional assessment of myocardial perfusion and coronary blood flow through recently developed various imaging and analytical methodologies.[2,49,484,485] However, CCTA may not always be sufficient to evaluate patients with arrhythmia or massive coronary artery calcification. In clinical practice, it is also required to have adequate knowledge of the side effects of contrast media and radiation exposure. The following section introduces the principles behind cardiac CT, image data acquisition and the related precautions, as well as the basic evaluation methods. Finally, it describes the new imaging technologies and methods of analysis.

### 12.1 Advances in Cardiac MDCT

The recent MDCT technology features (1) a wider detector, (2) high spatial resolution, (3) high temporal resolution, and (4) iterative reconstruction as well as advances in the associated technologies. All these factors contribute to improvements in both the image quality and the diagnostic performance of CCTA. The international joint guidelines recommend the specifications of MDCT systems for cardiac CT to perform appropriate CT examinations.[486]

#### 12.1.1 Wide-Coverage MDCT

Wide-coverage MDCT in the z-axis direction has the further advantage of reducing the image acquisition time. In fact, while a 64-row CT scanner (i.e., the minimum requirement for CCTA) can obtain coronary artery images in 5–8 s, the entire image of the heart is obtained in ≤1 s using the 256-row or 320-row CT scanners, because their detector width of 16 cm covers the whole heart with a single rotation of the tube. Shortening of the image acquisition time helps reduce the breath-holding time and heart rate variation during image acquisition. Therefore, it reduces banding artifacts and misalignment of the CT dataset, maintaining coronary artery continuity, which in turn contributes to good image quality.

#### 12.1.2 Temporal Resolution

Temporal resolution generally refers to the "discrete resolution of a measurement with respect to time" and is defined as the amount of time needed to revisit and acquire data for the exact same location on the CT image. Cardiac CT can obtain clear images of the heart and coronary arteries with a high temporal resolution. When ECG-gated scanning is performed, a 360-degree CT image can be reconstructed from the projection data with approximately half a rotation (actually 180 degrees + fan angle) of the X-ray tube using the half-reconstruction algorithm. Therefore, the temporal resolution is approximately half the speed of the X-ray tube rotation speed. The abovementioned guidelines also recommend the use of a MDCT system with a tube rotation speed ≤0.35 s for cardiac CT. Current available cutting-edge MDCT scanners are equipped with an even faster gantry rotation speed (0.25–0.28 s) and achieve better temporal resolution. In addition, a dual-source CT system has 2 X-ray tubes and 2 corresponding detectors (mounted onto the rotating gantry with an angular offset of 90 degrees), and can obtain the half-reconstruction images with double the temporal resolution.

When a single phase is reconstructed from a combination of several cardiac cycles using the multisector reconstruction algorithm, the time required for each imaging sector is reduced, and the temporal resolution is increased.

#### 12.1.3 Spatial Resolution

Spatial resolution refers to the distance between or the ability with which 2 different objects, which are either closely located or small in pixel size in a digital image, can be distinguished. Considering a 64-row CT can obtain CT images with a slice thickness of 0.5–0.625 mm, whereas some MDCT scanners can do so with a spatial resolution of 0.35 mm in the XY direction, the distortion-free CT volume data with isotropic voxels can be utilized in clinical practice. In addition to slice thickness, multiple other factors also influence the spatial resolution, including image parameters such as the tube voltage and tube current, gantry rotation speed, and the number of sampling views. Thus, CT vendors have aimed at improving the spatial resolution by taking into consideration the various features of each MDCT scanner. To date, spatial resolution has been improved by increasing in the number of sampling views through a fine tube focal spot deflection (double sampling) for the X-axis or Z-axis direction and/or high-speed data sampling.

Furthermore, an ultra-high resolution CT scanner launched in 2017 is capable of resolving the anatomy to 0.15 mm in the XY direction, resulting in fine volume data with a slice thickness of 0.25 mm. This shows promise for improving the diagnostic accuracy of small vessel disease, in-stent restenosis, and calcified lesions. Nevertheless, CCTA remains inferior to invasive coronary angiography in terms of both temporal and spatial resolution. In addition, several problems, including motion artifacts resulting from insufficient temporal resolution, misregistration artifacts because of improper segmental reconstruction, and beam hardening artifacts derived from high attenuation structures (e.g., stents and calcification), are yet to be overcome. Therefore, CCTA cannot completely replace invasive coronary angiography at present.

#### 12.1.4 Iterative Reconstruction

Up until recently, CT images have been mostly reconstructed with FBP, which can reconstruct CT images rapidly using a simplified model, but shows increased image noise. Iterative reconstruction is a method of image reconstruction in which a first estimate image is created and then errors between the calculated raw data by a forward projection step considering the system geometry and the measured raw data, followed by repeated updating of the reconstructed image so that errors are minimized. This technique decreases the image noise and can be used to improve the quality of images obtained with a normal radiation dose, as well as to maintain image quality with a lower dose CT scanning.

### 12.2 Image Acquisition and Image Reconstruction

#### 12.2.1 ECG-Gated Image Acquisition

The following 2 methods have been implemented for ECG-gated image acquisition: (1) retrospective and (2) prospective. In the former, the scanning is performed while simultaneously recording an ECG, and the CT images reconstructed from the target cardiac phase are obtained after scanning. In the latter, image acquisition (X-ray exposure) is performed only for a specific cardiac phase, which is set by the predetermined time from the R wave. Although retrospective ECG gating was the standard method in the early days of CCTA, its related increase in radiation exposure (the X-ray is exposed during the unneeded phases for evaluation) is concerning. To reduce the radiation dose, the X-ray exposure should be optimized to the required cardiac phase to obtain a still image according to the scan heart rate (dose modulation).

Prospective ECG-gated scanning minimizes radiation exposure because scanning (X-ray exposure) is only performed during a specified cardiac phase. Therefore, it has become the standard method of CCTA for the appropriate scan heart rate. Given that both the target heart rate and the cardiac phase depend on the temporal resolution of the MDCT scanner and image reconstruction method, knowledge of ECG-gated cardiac CT is essential. With regard to cardiac physiology, as the coronary and myocardial blood flow predominantly increase during diastole, image acquisition at mid-diastole is desirable (low heart rate), whereas the end-systolic phase is generally included in the acquired cardiac phase when the patient's scan heart rate is higher.[486]

#### 12.2.2 Noncontrast Cardiac CT

Noncontrast cardiac CT refers to ECG-gated noncontrast CT scanning and mainly evaluates the extent of coronary artery calcification. Conventionally, electron-beam CT was used to evaluate coronary artery calcification,[487,488] but recently MDCT can achieve similar accuracy after appropriate adjustment of the scanning conditions. Indeed, most MDCT scanners used for CCTA can satisfy these requirements. Specifically, prospective ECG-gated scanning, with a slice thickness of 2.5–3 mm, using a MDCT scanner with 4 or more detector rows and a gantry rotation speed of at least 0.5 s, are endorsed for the assessment of coronary artery calcification. Moreover, the target cardiac phase should be set at the early to mid-diastolic phase and scanning should be performed while the patient is breath-holding.[489]

#### 12.2.3 Contrast Injection Protocol

Adequate contrast enhancement of coronary arteries is essential for reliable evaluation using CCTA. Considering that optimal images require a high intra-arterial attenuation (>250 Hounsfield units [HU]), contrast medium with high iodine concentrations (270–400 mg iodine/mL) and intravenous administration (injection rate: 4–7 mL/s) are preferred in adults. A slower infusion rate may be acceptable in some patients with small body size, who can undergo low-voltage scanning. Generally, the duration of the contrast injection should be longer than the scanning time (≥10 s) and a 20G cannula should be used.[486]

Intracoronary attenuation significantly modifies the attenuation of coronary atherosclerotic plaques assessed with CCTA. Therefore, the protocol for contrast injection should be modified to achieve appropriate CT values.[490] Because the patient's body size (body weight and body surface area) and cardiac function also influence contrast enhancement, collecting relevant information from the patient prior to the cardiac CT examination is recommended.[486]

#### 12.2.4 Premedication

Appropriate premedication of the patient is helpful to

obtain high-quality CT images with most of the current MDCT scanners. This section outlines the use of $\beta$-blockers and nitrates for heart rate control and clear coronary artery delineation, respectively. The use of $\beta$-blockers for heart rate control has 2 advantages: (1) lowering the scan heart rate, which allows for still images and (2) allows the use of prospective ECG-gated scanning to minimize radiation exposure.

Beta-blockers are selected by considering the drug's half-life as well as $\beta$1-selectivity (to reduce the risk of provoking asthma). They are generally administered either orally or intravenously. For example, metoprolol (a $\beta$1-selective agent) is administered orally at 1 hour before CT examination, at a dose of 20–100 mg, depending on the patient's body weight and baseline heart rate. In the case of insufficient effect, additional metoprolol may be given either orally or intravenously at the time of examination. In contrast, landiolol hydrochloride is a $\beta$1-selective intravenous drug with a short half-life (≈4 min; its use for CCTA is covered by insurance in Japan). It can be administered immediately before scanning in the CT room, given its short-acting effect.

Nitrates act directly on the vascular smooth muscle to dilate coronary arteries, thus contributing to an improvement in coronary artery stenosis diagnosis. Either sublingual nitroglycerin tablets (0.3 mg/tablet) or sublingual sprays (0.3 mg/dose) are used. Considering that the heart rate transiently increases immediately after administration, nitrates are preferably given 5 min prior to CCTA. When used at the same dose, sublingual sprays exert a stronger vasodilatory effect than sublingual tablets. Furthermore, sublingual tablets should be used with caution because their absorption can be variable. Accordingly, the administration of 2 puffs of sublingual spray (0.6 mg: equivalent to 1 mg of isosorbide dinitrate by intracoronary administration) is recommended. Contraindications to nitrates include severe hypotension, severe aortic stenosis, and angle closure glaucoma, as well as patients taking phosphodiesterase inhibitors.

### 12.2.5 Scan Timing

A 64-row (or more) MDCT can reduce the image acquisition time and the amount of contrast medium required. However, it is essential to use the optimal scan timing. In addition to the contrast injection protocol, the optimal scan timing should be based on the scanning duration (the field of view) time as well as patient-related factors (body size and cardiac function). At present, scan timing of CCTA is determined by either bolus tracking or timing bolus (also referred to as "test injection").

Bolus tracking is an automatic triggering method. Briefly, after the administration of the contrast medium for the main scan, contrast enhancement is monitored in a region of interest set on the aorta. When the aortic attenuation reaches a predetermined threshold, scanning starts. This method is simple; however, some difficulty remains in both reducing the dose of contrast medium and in determining the optimal scan timing for scanning in patients with cardiac dysfunction. Timing bolus involves the administration of a small dose of contrast medium prior to the main scan for in-advance evaluation of the optimal scan timing. Using the time-attenuation curve of the timing bolus scan, this method is helpful to both objectively determine the optimal scan timing and reduce the amount of contrast medium used for the main scan.

### 12.2.6 Image Reconstruction

Spatial resolution of CT images is influenced by both the specifications of MDCT (e.g., slice thickness and number of sampling views) and the image reconstruction. In the process of image reconstruction that generates tomographic images from X-ray projection data, CT images are generated through the abovementioned FBP or iterative reconstruction method. In addition, this is combined with dedicated filtering processes (i.e., reconstruction kernel, also referred to as the "filter"). Although CT images for CCTA are generally reconstructed with a smooth vascular kernel, a sharper kernel that handles high-frequency data is applied when assessing calcified lesions or coronary stents. Although the images reconstructed with a sharp kernel have better spatial resolution, increased noise is produced. Therefore, a sharp kernel is not suitable for the evaluation of structures with low CT values such as noncalcified plaques.[486]

## 12.3 Radiation Exposure

A European epidemiology group reported that Japan had the highest risk of cancer attributable to diagnostic X-ray (i.e., 3.2% among 15 developed countries).[491] Similarly, another report discussed the risk of developing cancer as a result of CCTA using 64-row scanners.[492] Given that most cardiac CT requires thin slices and a highly overlapping scan, the radiation exposure to the field of view is relatively high. Here we outline the basic characteristics and management of radiation exposure, as well as its reduction.

### 12.3.1 Radiation Protection and Management

Radiation protection is based on the application of 3 principles: justification, optimization, and limitation. Justification suggests that "no practice involving exposure to radiation should be adopted unless it produces sufficient benefit to the exposed individual or to society to offset the detriment it causes". In contrast, optimization implies that "exposure to radiation should be as low as reasonably achievable'. With regard to the medical exposure of patients to radiation, applying dose limits or constraints is not appropriate, given that limits would often do more harm than good. However, considering the potential benefits of CT examinations, making an effort to optimize and reduce the radiation dose is essential.[493]

### 12.3.2 Exposure Dose Unit and Evaluation Methods

Radiation exposure can be assessed through both the absorbed dose and the effective dose. Although the absorbed dose (expressed in Gy) can be measured using a dosimeter, managing it in clinical practice is difficult. Furthermore, several indices can be used to estimate the absorbed dose, including the CTDIvol and the DLP.[494] The CTDIvol is a numerical value (expressed in mGy) that is calculated by integrating over the dose profile for a single axial rotation, then dividing by the nominal beam width. In contrast, the DLP is the product of the CTDIvol and the scan length of a group of scans (expressed in mGy·cm). These parameters are generally listed in the dose reports for MDCT scanners. The effective dose (expressed in Sv) is the product of the DLP and a weighting factor for the target region of the scanning. This index is adopted when comparing the risk of radiation exposure between CT and other imaging modalities.

### 12.3.3 Risks of Radiation Exposure Associated With CT

Radiation exposure is known to produce a wide variety of biological damage. Although radiation doses >100 mGy clearly increase the incidence of cancer in humans, evidence that lower doses increase the risk of cancer is lacking. Nonetheless, not to underestimate the risk of radiation exposure, the potential risk of carcinogenesis should be considered even at the lowest dose (the linear no-threshold hypothesis). However, with exposure to doses exceeding 100 mSv, the approximated overall fatal risk coefficient of developing cancer is estimated to increase at a rate of 0.5% per 100 mSv. In contrast, a recent epidemiological study estimated that the lowest carcinogenic dose was 10–50 mSv for acute exposure and 50–100 mSv for chronic exposure.[495]

### 12.3.4 Factors Influencing the Radiation Dose

#### a. Scan Parameters

These parameters include the X-ray tube voltage, tube current, gantry rotation speed, and pitch. With the standard tube voltage of 120 kV, the guidelines of the Society of Cardiovascular Computed Tomography (SCCT) recommend low-voltage scanning combined with an iterative reconstruction technique, as mentioned earlier. For example, a tube voltage of 100 kV is recommended for patients with either a body weight ≤100 kg or a BMI ≤30 kg/m$^2$, whereas a voltage of either 100 kV or 80 kV is recommended for children and adults with a small body size.[486] Note that the tube current should be adjusted according to both the patient's size and the target organ. The radiation exposure increases if a greater overlapping scan is performed using a smaller helical pitch.

#### b. Image Quality and Radiation Exposure

Generally, image quality is closely proportional to the radiation dose; that is, as the radiation dose decreases, the image quality decreases. When other factors interfere with image quality, increasing the radiation dose is necessary. Therefore, it is important to minimize the radiation dose while avoiding a remarkable decrease in image quality. In young patients (children) and women, who are particularly susceptible to radiation and may have a higher lifetime risk of cancer, the indications for CT examinations should be carefully considered.[496]

According to previous reports, radiation exposure in CCTA is approximately 8–15 mSv, which is higher than that observed with invasive coronary angiography (3–6 mSv). Other previous studies suggested that CCTA combined with dose automatic modulation, as well as a noise reduction filter, resulted in decreased radiation exposure (≈3–8 mSv). Depending on the patient's size and scan heart rate, the abovementioned techniques to minimize radiation exposure can be combined with the latest CT technologies (e.g., area-detector CT or dual-source CT) and reduce the radiation dose for CCTA to around 1–3 mSv.

## 12.4 Adverse Reactions to Contrast Medium

### 12.4.1 Allergic Reactions

Adverse reactions to iodinated contrast medium occur in approximately 3% and 0.04% of patients, who develop mild and severe symptoms, respectively. Furthermore, life-threatening adverse reactions affect 1 in 170,000 patients.[497] Initial screening for risk factors associated with serious adverse reactions is essential and includes the patient's history of allergy (atopy and food allergy, etc.), which is associated with an approximately 2-fold increase in the incidence of reactions; history of bronchial asthma (≈10-fold increase); previous moderate or severe reaction to a contrast agent (≈4- to 5-fold increase); and serious heart disease (≈3-fold increase).[498] Although compliance with institutional guidelines is required, contrast medium should be administered carefully in patients with a history of noncontrast allergic reactions. It is contraindicated for patients with asthma, prior moderate/severe contrast agent reaction, or serious heart disease. Serious contrast allergic reactions can occur even in patients who did not present any adverse reaction during previous contrast CT examinations. Therefore, the CT room has to be staffed with appropriately trained personnel and should include an emergency cart equipped with commonly used drugs (adrenaline and H1 blocker anti-histamines) to promptly handle contrast allergic reactions.

### 12.4.2 Contrast-Induced Nephropathy and CKD

According to the 2012 joint committee guidelines, contrast-induced nephropathy (CIN) is defined as an "increase in serum creatinine (Cr) by ≥25% from baseline or by ≥0.5 mg/dL within 72 hours after contrast administration".[499] Use of the eGFR is recommended for the assessment of renal function ($eGFR = 194 \times Cr^{-1.094} \times age^{-0.287}$ [×0.739 for women]). Specifically, eGFR and urinary protein are used to classify CKD. Generally, patients with impaired renal function are more likely to develop acute renal failure due to CIN after contrast administration. Therefore, the guidelines also recommend contrast-enhanced CT to be performed carefully with precautions for patients with an eGFR <45 mL/min/1.73 m$^2$. Examples include reducing the amount of contrast medium or giving a preventive saline infusion. With regard to high-risk patients, an intravenous saline infusion at 1 mL/kg/h is generally recommended 6 hours prior to and 6–12 hours following the administration of the contrast agent.[499]

For diabetic patients, discontinuing biguanides 48 hours prior and 48 hours following the administration of the contrast medium is suggested, because biguanides may provoke lactic acidosis due to drug interaction.[499] In addition, an increase in the risk of CIN may be observed in patients with dehydration, diabetes mellitus, congestive heart failure, or renal dysfunction, as well as in elderly patients. Previous studies also report that CIN is associated with increased mortality, including death from recurrence of CAD.[500]

Although $\beta$-blockers are widely used in CCTA, a previous study suggested an increase in the incidence and seriousness of adverse reactions to contrast medium in patients receiving premedication with $\beta$-blockers.[501] However, given that the study population involved patients with cardiac disease, further investigations are required to clarify whether $\beta$-blockers increase the risk of reactions to contrast medium in patients undergoing routine CCTA. Incidentally, anaphylactic reactions to the contrast medium are sometimes refractory to the usual dose of epinephrine in patients taking $\beta$-blockers. Therefore, it is important to know that glucagon may benefit patients with severe adverse reactions to contrast medium.[502]

## 12.5 Indications (Table 33)

Several professional societies and joint committees have proposed appropriate use criteria regarding CCTA in a

variety of clinical scenarios: (1) general use of cardiovascular CT,[484] (2) CCTA in patients with chronic chest pain (including other diagnostic tests),[503,504] and (3) multimodal diagnostic tests for stable coronary heart disease.[505] The SCCT has suggested CCTA guidelines on radiation dose and dose-optimization strategies,[506] the scanning protocol,[486] as well as the interpretation and reporting.[485]

The Japanese Circulation Society and the multi-societies joint working groups published both the Guidelines for Noninvasive Diagnosis of Coronary Artery Lesions (JCS 2009)[2] and the Guidelines for Diagnostic Evaluation of Patients with Chronic Ischemic Heart Disease (JCS 2010).[49] These describe the basics behind CCTA and its clinical applications.

Given that CCTA involves a risk of radiation exposure and adverse reactions to the contrast medium, the indications must be individually and carefully considered. The most appropriate candidates for such an assessment are symptomatic patients with suspected stable coronary artery disease, who have an intermediate pretest probability and present uninterpretable ECG or any difficulties with exercise stress testing. On the other hand, it is not appropriate to perform CCTA in asymptomatic patients, who have a low pretest probability, or present interpretable ischemic ECG changes in addition to de novo patients, CCTA may also be useful in patients who have undergone prior revascularization therapy (e.g., CABG or coronary stenting with stent diameter ≥3 mm[507,508]), and to those with known or suspected congenital coronary artery anomalies.[509]

Estimating the pretest probability plays an important role in the diagnostic testing for coronary artery disease. The following 2 methods are mainly used to determine such a probability. One method is based on large-scale epidemiological studies conducted in the USA using several factors, including age, sex, symptoms, and coronary risk factors (Duke score or Framingham risk score). The other method is based on a Japanese epidemiological study (NIPPON DATA) that can calculate the 10-year risk of death from stroke and coronary artery disease, including myocardial infarction and angina pectoris.[510–512]

## 12.6 Noncontrast Cardiac CT

### 12.6.1 Coronary Artery Calcification

Coronary artery calcification is a pathogenic process occurring during stabilization of atherosclerotic plaques, forming as a result of chronic vascular inflammation and metabolic factors. The extent of coronary artery calcification correlates with the severity of coronary atherosclerosis, and can be used to predict future cardiovascular events.[513]

**Table 33. Recommendations and Levels of Evidence for CCTA**

**1. Asymptomatic**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **CACS (risk stratification)** | | | | |
| Low pretest probability of CAD | III | C | C2 | VI |
| Intermediate pretest probability of CAD | IIa | A | B | II |
| High pretest probability of CAD | IIa | A | B | II |
| **CCTA (detection of coronary artery stenosis)** | | | | |
| Low pretest probability of CAD | III | C | C2 | VI |
| Intermediate pretest probability of CAD | III | C | C2 | VI |
| High pretest probability of CAD | IIb | C | C1 | VI |

**2. Symptomatic or clinical scenario equivalent to myocardial ischemia**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **CCTA (detection of coronary artery stenosis)** | | | | |
| Low pretest probability of CAD, ECG uninterpretable or unable to exercise | I | A | A | I |
| Intermediate pretest probability of CAD, ECG uninterpretable or unable to exercise | I | A | A | I |
| High pretest probability of CAD, ECG uninterpretable or unable to exercise | IIa | B | B | II |
| Suspected vasospastic angina | III | C | C2 | VI |
| **Unstable angina/non-ST-elevation acute myocardial infarction** | | | | |
| Low-to-intermediate likelihood (no ECG ischemic change, biomarker test negative) | IIa | B | A | II |
| High likelihood (ECG ischemic change, biomarker test positive) | III | C | D | VI |

(**Table 33** continued the next page.)

| 3. Combined assessment | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **CCTA (detection of coronary artery stenosis)** | | | | |
| Abnormal or uninterpretable prior ECG test | I | A | B | III |
| Mildly abnormal or equivocal results in stress MPI | IIa | B | B | III |
| **Stress CTP (assessment of myocardial ischemia)** | | | | |
| Non-diagnostic results or moderate or more stenosis in CCTA | IIa | B | B | II |
| Assessment of myocardial ischemia using stress CTP alone | IIa | B | B | II |
| **Myocardial infarction imaging with the late image** | | | | |
| As an alternative when SPECT or MRI is not available | IIb | C | C1 | IVa |

| 4. Other clinical scenarios | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Screening of CAD in patients diagnosed with heart failure | IIb | B | C2 | VI |
| **Follow-up for postrevascularization and other clinical scenarios** | | | | |
| Post-CABG | IIa | B | B | I |
| Post-PCI (coronary stent >3 mm in diameter) | IIa | B | B | IVa |
| Post-PCI (coronary stent ≤3 mm in diameter) | IIb | B | D | IVa |
| Post-PCI (plain dilation alone, directional or rotational coronary atherectomy) | IIa | B | C1 | VI |
| Pre-operative evaluation for cardiac surgery | IIa | B | B | IVb |
| Pre-operative evaluation for noncardiac surgery | IIb | C | C2 | IVb |
| Coronary lesions (aneurysm) in Kawasaki disease | IIa | C | C1 | IVb |
| Congenital coronary anomaly | I | B | B | I |
| Screening of CAD in medical checkup | III | C | C2 | VI |

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; COR, class of recommendation; CTP, CT perfusion; GOR, grade of recommendation; LOE, level of evidence.

For example, Agatston et al identified significant calcified lesions determined by a CT value ≥130 HU and a size ≥2 pixels. They defined the summed area score of each calcified area multiplied by an attenuation factor, according to the maximal CT value of the lesion, as CACS or AS.[514] Specifically, the CACS can be quantified by the following 3 methods: AS, volume score, and mass score. Although age, sex, and ethnicity influence the prevalence and extent of CACS, some studies have reported CACS as both an independent predictor of future cardiovascular events and a useful diagnostic tool combined with the pretest probability for reclassification of patients suspected of CAD.[515–518] Several guidelines and expert consensus suggest that both CACS-based risk stratification and treatment modification are effective in asymptomatic patients up to an intermediate-risk probability. Further evidence is needed to determine whether all patients should undergo CACS testing.[505,519,520]

### 12.6.2 Visceral Fat and Pericardial Fat

Adiponectin is a hormone that promotes insulin sensitivity and has an anti-inflammatory effect. Abundant visceral and pericardial fat results in reduced adiponectin secretion and induces atherosclerosis (caused by various inflammatory cytokines secreted from adipose tissue). Recent studies have demonstrated that pericardial fat is a significant risk factor for future coronary events independent of traditional coronary risk factors and the CACS, providing complementary information from noncontrast cardiac CT.[521]

### 12.6.3 Fatty Degeneration in the Myocardium

Fatty degeneration (also called fat deposition) in the myocardium can be observed in patients with OMI and cardiomyopathy. Fatty degeneration develops over time during the occurrence of myocardial necrosis, damage, or fibrosis.[522] When it is observed predominantly in the subendocardial layer corresponding to the territory of a coronary artery, it is suggestive of OMI.

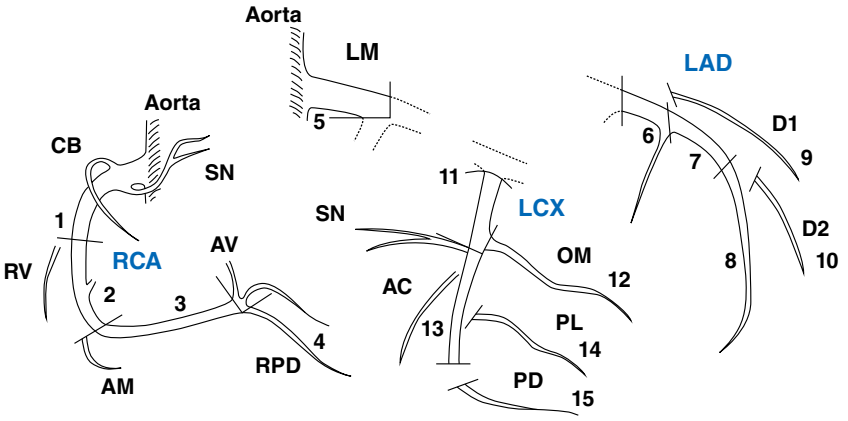



**Figure 9.** Coronary artery segment model according to the AHA classification. Main coronary vessels: LM, left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary. Major branches: D1, first diagonal branch; D2, second diagonal branch; OM, obtuse marginal branch; PL, posterolateral branch; PD, posterior descending branch; RPD, right posterior descending branch. Minor branches: AC, atrial circumflex branch; AM, acute marginal branch; AV, atrioventricular node branch; CB, conus branch; RV, right ventricular branch; SN, sinus node branch. The intermediate branch artery is generally assigned to segment number 16. (Reproduced from Austen et al 1975,[524] with permission. Copyright (1975) by American Heart Association.)

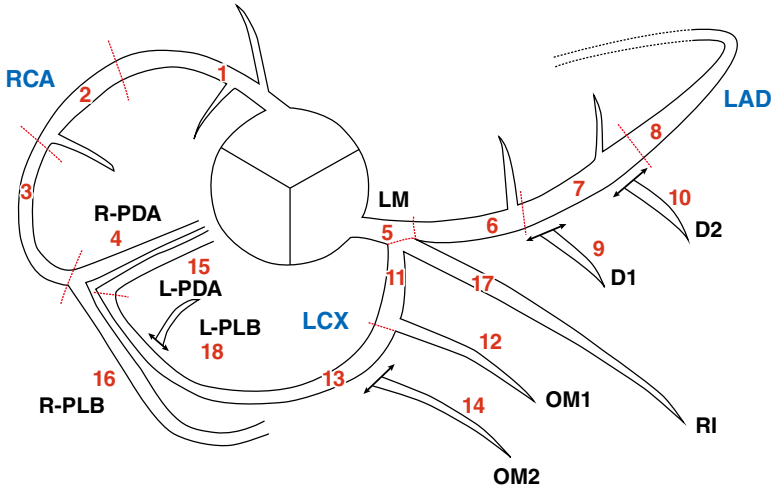



**Figure 10.** Coronary segmentation diagram of the Society of Cardiovascular Computed Tomography (SCCT). Main coronary vessels: LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; RCA, right coronary. Major branches: D1, first diagonal branch; D2, second diagonal branch; OM1, first obtuse marginal branch; OM2, second obtuse marginal branch; L-PLB, posterolateral branch from LCX; R-PLB, posterolateral branch from RCA; L-PDA, posterior descending branch from LCX; R-PDA, posterior descending branch from RCX; RI, ramus intermedius. (Reproduced from Leipsic et al 2014,[485] with permission from Elsevier. Copyright (2014) by Society of Cardiovascular Computed Tomography.)

## 12.7 Interpretation and Reporting of CCTA

### 12.7.1 Analysis

CCTA should be analyzed and reviewed using dedicated workstation software for 3-dimensional assessment of the heart. Given the complexity of coronary artery anatomy, observing multiple cross-sectional images and various image formats is important. The interpreters should be familiar with the basics of CT image reconstruction, the use of workstations, and the advantages and limitations of the displayed image formats. The SCCT guideline recommends appropriate image reformats for the assessment of CCTA (**Figure 8**), as follows: "Recommended" (axial tomogram, multiplanar reformations [MPR], and maximum intensity projections [MIP]); "Optional" (curved planar reformations [CPR]), and "Not recommended" (volume

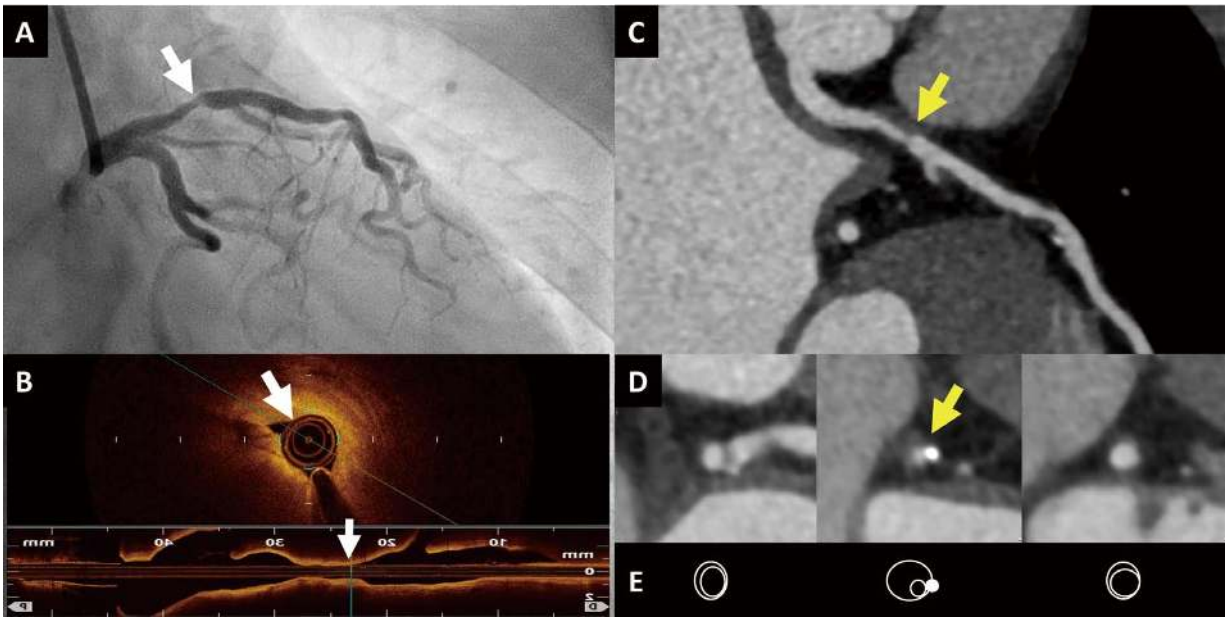



**Figure 11.** Dataset of a man in his 60 s, who presented with exertional angina. (**A**) Invasive coronary angiography; (**B**) OCT; (**C**) CCTA (curved planar reformat image); (**D**) CCTA (multiplanar reformat=cross-sectional images); (**E**) Schemas of a cross-sectional image in CCTA. The outer and inner rims of the coronary arterial wall including coronary plaque are presented (white line) and the coronary artery calcification (based on the original CT image). CCTA described a moderate stenosis (50–69% stenosis in diameter) with positive remodeling and spotty calcification. Both invasive coronary angiography and OCT verified the findings.

rendering [VR]).[485] An angiographic view that allows the cardiac chambers to be viewed without contrast medium is useful for the MIP image format.[523] Although the VR image reformat is not suitable for quantification of coronary stenosis severity, it allows an east review of the entire heart, including coronary anatomy and stenotic lesions.

### 12.7.2 Coronary Anatomy

CCTA provides 3D images that facilitate the understanding of the anatomical relation between coronary arteries and the surrounding structures, as well as of the origin and course of coronary arteries, their branches, and coronary dominance.[485] The use of CCTA will be most beneficial to patients with coronary anomalies.

Coronary artery segmentation is necessary for accurate description in the report and is commonly based on either the AHA model or the SCCT model (**Figures 9**,**10**).[485,524] The SCCT model has adopted some modifications of the AHA model, including the variations in the anatomy of the distal right and circumflex coronary arteries. Both models are easy to use because of their systematic nature. It is desirable to standardize the segmentation classification and reporting used at each center (i.e., between the attending physicians and diagnosticians).

### 12.7.3 Coronary Artery Stenosis

When coronary artery stenosis is evaluated with CCTA, the stenosis severity is assessed by measuring the luminal diameter of the stenotic region and of the nearby healthy proximal and distal sites on the cross-sectional images. For accurate evaluation, observing multiple display images in a complementary manner is useful (**Figure 11**). A meta-analysis demonstrated that the diagnostic ability of 64-row CT or dual-source CT for coronary artery stenosis (>50%) was sufficient for excluding significant stenosis with a sensitivity of 89%, specificity of 96%, positive and negative predictive values of 78% and 98% (**Table 34**).[525–536] Although the quantitative assessment of CCTA is generally well correlated with that of invasive coronary angiography and IVUS, relatively large standard deviations are seen (±25% at best).[485]

Accordingly, the SCCT guidelines recommend a stepwise evaluation of the stenosis (**Table 35**).[485] With regard to the morphological assessment of coronary artery stenosis (≥50%) using CCTA, a 5-year follow-up international registry of 1,884 patients from 12 centers showed an association between an increase in the number of significant CAD and a higher incidence of future cardiac events. Similarly, it has been suggested that the event rate in patients with significant (36.3%) or nonsignificant (13.2%) stenosis was significantly higher than that in patients without coronary lesions (5.6%).[537]

The assessment of coronary artery stenosis and myocardial ischemia is essential for both identification of the culprit lesion and decision-making for coronary revascularization. A single-center study reported that the sensitivity and specificity of CCTA (≥50% stenosis) to detect hemodynamically significant CAD (invasive FFR <0.8) were 45% and 79%, respectively.[538] In contrast, when myocardial ischemia assessed by stress myocardial perfusion imaging by SPECT (PET) was defined as the reference standard, previous data from multiple centers described the positive and negative predictive values of CCTA (≥50% stenosis) as 29–44% and 88–100%, respectively.[539] Therefore, single

**Table 34. Diagnostic Performance of 64-Slice CT and Dual-Source CT for Detection of Significant Coronary Stenosis (Luminal Diameter >50%) on a Per-Segment Basis**

| | No. of patients | No. of segments | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| Leschka et al[526] | 67 | 1,005 | 94 | 97 | 87 | 99 |
| Leber et al[527] | 55 | 732 | 76 | 97 | 75 | 97 |
| Raff et al[528] | 70 | 1,065 | 86 | 95 | 66 | 98 |
| Mollet et al[529] | 51 | 725 | 99 | 95 | 76 | 99 |
| Ropers et al[530] | 81 | 1,128 | 93 | 97 | 56 | 100 |
| Schuijf et al[531] | 60 | 854 | 85 | 98 | 82 | 99 |
| Ong et al[532] | 134 | 1,474 | 82 | 96 | 79 | 96 |
| Ehara et al[533] | 69 | 966 | 90 | 94 | 89 | 95 |
| Nikolaou et al[534] | 72 | 1,020 | 82 | 95 | 69 | 97 |
| Weustink et al[535] | 77 | 1,489 | 95 | 95 | 75 | 99 |
| Leber et al[536] | 88 | 1,232 | 94 | 99 | 81 | 99 |
| **Total** | **824** | **11,690** | **89** | **96** | **78** | **98** |

All values are expressed as percentages with absolute numbers in parentheses. Sensitivity and specificity were calculated only for evaluable segments. CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value. (Reproduced from Schroeder et al 2008,[525] with permission of Oxford University Press on behalf of the European Society of Cardiology. OUP and the ESC are not responsible or in any way liable for the accuracy of the translation. The Japanese Circulation Society is solely responsible for the translation in this publication/reprint.)

**Table 35. Recommended Stenosis Grading**

| | | |
|---|---|---|
| 0 | Normal | Absence of plaque and no luminal stenosis |
| 1 | Minimal | Plaque with <25% stenosis |
| 2 | Mild | 25–49% stenosis |
| 3 | Moderate | 50–69% stenosis |
| 4 | Severe | 70–99% stenosis |
| 5 | Occluded | |

(Reproduced from Leipsic et al, 2014,[485] with permission from Elsevier. Copyright (2014) by the Society of Cardiovascular Computed Tomography.)

evaluation by CTA is often insufficient to determine the indications for revascularization therapy, although CCTA is useful for excluding significant CAD lesions with myocardial ischemia. In the case of ≥50% CTA-stenosis or nondiagnostic CTA testing, considering a functional assessment (e.g., noninvasive stress myocardial perfusion imaging for the evaluation of myocardial ischemia) is recommended.[505]

### 12.7.4 Coronary Plaque

CCTA can evaluate extraluminal plaques associated with vascular remodeling and can be used to differentiate plaque subtypes (e.g., calcified, noncalcified, and partially calcified plaque). The SCCT medical terminology guidelines recommend using "noncalcified" plaque composition, rather than "soft" or "lipid-rich", because the low intraplaque CT values do not always correlate with the pathological findings.[540] Recent CCTA studies described vulnerable plaque ("high-risk plaque") characteristics that are independently associated with future ACS. They include (1) low-attenuation plaque <30 HU, (2) positive remodeling >1.1, (3) "napkin-ring" sign, and (4) spotty calcium deposits. When ≥2 of these findings are present, it should be reported as high-risk plaque.[540–542] A Japanese multicenter study of 2,802 patients suggested that the 2-year rate of cardiac events in patients without plaque, with coronary calcification alone, or with noncalcified or partially calcified plaques was 0.2%, 2.0%, and 2.1%, respectively, which indicates the importance of CTA-based plaque assessment.[543]

### 12.7.5 Cardiac Function (Optional)

When retrospective ECG-gated data acquisition is performed, multiphase reconstruction can generate a series of single cardiac cycle at 5% or 10% intervals. This enables cardiac functional analysis from the structure and wall motion of the ventricles, atrium and cardiac valves for quantitative assessment of left ventricular (LV) EDV, ESV, LVEF, and LV mass.[544] If a $\beta$-blocker is administered to reduce the scan heart rate, it should be done with caution because reduced myocardial contractility results in increased LVESV and reduced LVEF and cardiac output.[545]

### 12.7.6 Noncoronary and Extracardiac Findings

In addition to the coronary anatomy, cardiac CT enables simultaneous assessment of the surrounding noncoronary and extracardiac structures (e.g., cardiac valves, myocardium, aorta, and superior/inferior vena cava, and the field of view includes parts of the lungs, mediastinum, and digestive organs). Reviewing all the visible findings is essential because (1) primary or secondary lesions from noncoronary disease may be detected and (2) noncardiovascular disease may become the final diagnosis.[485] Triple-rule-out CTA for acute chest pain can be an effective evaluation of acute myocardial infarction, aortic dissection and pulmonary thromboembolism. Two-phase CT is a reliable method for detecting intracardiac thrombi, including the left atrial appendage, in patients with a history of cardiac dysfunction or arrhythmia.

In addition, the systematic evaluation and diagnostic algorithm of extracardiac findings from further evaluation to follow-up should be considered, as some patients with high pretest probability of CAD may overlap with those presenting extracardiac findings including malignant neoplasm.[546,547] From the viewpoint of radiation exposure

reduction, narrowing the field of view and maximizing the range of reconstruction images are desirable to allow the evaluation of optimized images.

### 12.7.7 Coronary Artery Disease Reporting and Data System (CAD-RADS)

Since 2016, a reporting system for CAD using cardiac CT has been proposed by 3 academic societies, based on the SCCT guidelines.[542] The CAD-RADS classifies the stenosis severity of CAD lesions using a 6-point scale (from 0, no stenosis to 5, occluded) as the interpretation in the report and provides patient-specific recommendations with common terms and reporting phrases. The recommendations for further testing for stable and acute chest pain are based on the outcomes of several recent large-scale multicenter studies. The CAD-RADS is promising with regard to improving consistency in patient care by both facilitating communication among healthcare professionals and accumulating the data for education and clinical research.

## 12.8 Functional Evaluation and New Technologies

In addition to morphological assessment of coronary artery stenosis and plaque, some researchers and clinical studies have been investigating functional assessment using cardiac CT and some diagnostic tools have already been established. This section will introduce the functional assessments and new technologies beyond conventional assessment using CCTA.

### 12.8.1 Image Fusion

Cardiac image fusion (hybrid imaging) can be obtained using a combination of anatomical (coronary anatomy and stenosis) and functional (e.g., myocardial perfusion imaging or metabolic imaging) information by 3-dimensionally superimposing CCTA and SPECT (or PET).[548] Some studies have demonstrated that image fusion is beneficial for decision-making and prognostic evaluation. However, it is controversial whether this method is clinically beneficial in terms of added value, relative to the increased radiation exposure and costs using CT and radionuclide examinations.[263,549] Nevertheless, image fusion may be helpful for further investigating the anatomical relationship between CTA-based coronary artery stenosis and SPECT-derived dysfunction territory such as in myocardial ischemia.

### 12.8.2 CT Perfusion

Cardiac CT can also evaluate myocardial ischemia by assessing the contrast enhancement of the myocardium (CT perfusion: CTP) during pharmacological stress (e.g., ATP, adenosine, etc.).[550] The methods used are generally dependent on the detector-range of MDCT and the number of data acquisitions. Static CTP imaging can evaluate myocardial ischemia with a hypo-enhanced (hypoperfusion) area in a snapshot (single-volume dataset) during the first-pass perfusion of contrast medium. In contrast, dynamic CTP can evaluate myocardial ischemia with quantitative parameters, including myocardial blood flow. This is possible by analyzing the time-attenuation curve of the myocardium using wide-detector MDCT, ideally covering the entire left ventricle. Many single-center and multicenter studies have shown that (1) stress CTP can detect significant CAD lesions and myocardial ischemia with noninferior ability to SPECT and MR, (2) stress CTP can add value to CCTA, and (3) the diagnostic ability for myocardial ischemia is equivalent between adequately performed static CTP and dynamic CTP.[551–555]

Cardiac CT can also describe myocardial infarction as either a perfusion defect in the early phase or as late iodine enhancement (LIE) in the late phase (e.g., after 5–8 min), allowing for assessment of myocardial viability.[556,557]

The SCCT guidelines[485] refer to the clinical effectiveness of stress CTP for detecting significant CAD lesions with high diagnostic performance. Stress CTP is a promising tool for further evaluation of patients with moderate or more coronary stenosis or nondiagnostic lesions using a single modality. In addition, it presents an alternative to stress myocardial perfusion imaging (e.g. SPECT).[551–554] However, stress CTP is not always necessary for all patients who undergo CCTA. If CCTA and stress CTP are performed in a single session, low-dose scanning should be applied in a comprehensive protocol, taking into consideration the issues associated with increased radiation exposure and contrast dose.[551,555]

### 12.8.3 Dual-Energy CT

Dual-energy CT creates 2 views (2 different CT attenuation images) per location at 2 different energies (e.g., 2 different tube voltages) and can characterize the chemical composition of a material. Dual-energy CT scanning can be performed with several technologies, including dual-source CT, high-speed tube voltage switching (rapid kV switching), and dual-layer CT. Some studies have suggested that dual-energy CT can evaluate both myocardial ischemia by calculating the contrast concentration in the myocardium (i.e., myocardial blood flow) and myocardial infarction by increasing the LIE in the late images.[558,559]

### 12.8.4 FFR-CT

FFR-CT is a novel simulation algorithm to calculate coronary flow and pressure fields in a hyperemic state from static CT images using computational fluid dynamics, image-based modeling, and cardiac physiology. The algorithm estimates the resting coronary blood flow and microvascular resistance using accurate anatomy of the coronary arteries and left ventricle. Furthermore, it assumes a hyperemic state during virtual pharmacological stress loading and hemodynamic change, to calculate the pressure difference across a coronary artery stenosis, which corresponds to invasive FFR as a ground truth[560–563] (see section "**13. Fractional Flow Reserve (FFR)-CT**" for details).

### 12.8.5 New Technologies

Some research groups have investigated the feasibility of new technologies such as subtraction CCTA for calcified lesions,[564] transluminal attenuation gradient (TAG) of CCTA,[565] and automatic quantification of CTA-based coronary artery territory mapping.[566] Although all the technologies are promising, further investigation is needed to ensure their clinical applications.

# 13. Fractional Flow Reserve (FFR)-CT

## 13.1 Background

Measurement of FFR enables prediction of the effect of coronary revascularization. The cutoff value for FFR was initially reported to be 0.75,[567–569] which showed the best correlation with stress tests such as stress myocardial

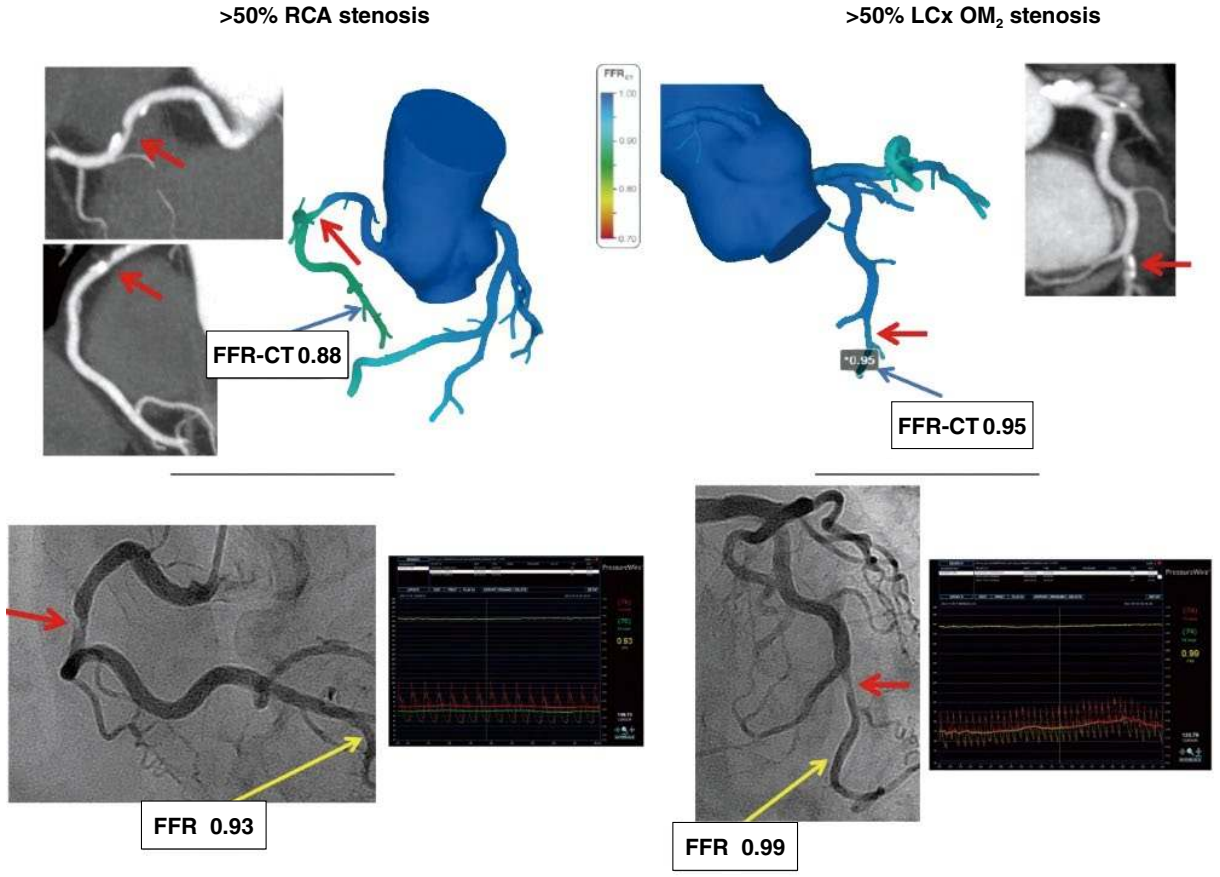



**Figure 12.** A 65-year-old Japanese male with abnormal ECG underwent CCTA, FFR-CT and invasive FFR (patient in the NXT trial). CCTA presented >50% stenosis of the right coronary artery (RCA) and the left circumflex (LCx) artery second obtuse marginal branch (OM2). However, FFR-CT showed no ischemia, with RCA FFR-CT=0.88 and LCx OM2 FFR-CT=0.95. Invasive FFR confirmed that the lesions were nonischemic, with FFR=0.93 in the RCA and FFR=0.99 in the LCx OM2. (Reproduced from Miyoshi et al 2015,[573] with permission.)

scintigraphy, but the value used currently ranges from 0.75 to 0.80.[570,571] The FAME trial (n=1,005) showed that FFR-guided (cutoff value: 0.8) PCI was associated with a significantly lower incidence of major cardiovascular events than standard PCI based on the extent of stenosis revealed by invasive coronary angiography (13.2% in the FFR-guided PCI group vs. 18.3% in the standard PCI group, P=0.02),[314] and that the cost of care during the 1-year follow-up was significantly lower with FFR-guided PCI than standard PCI (14,315 USD vs. 16,700 USD, P<0.001).[572]

In addition, the FAME 2 study (n=1,220) revealed that treatment of myocardial ischemia detected by FFR with PCI and optimal drug therapy was associated with less emergency revascularization than optimal drug therapy alone (1.6% vs. 11.1%, P<0.001).[315] However, measuring FFR with a pressure wire during cardiac catheterization requires intravenous or intracoronary drug administration to induce maximal hyperemia, adds to the time and cost of investigation, and is an invasive procedure associated with catheter manipulation. Against this background, FFR-CT has recently been developed as a method for noninvasively calculating the FFR by applying fluid dynamics to data from CCTA (**Figure 12**),[573] and it is becoming an option for assessment of myocardial ischemia in Western countries.

## 13.2 Basic Concept

FFR-CT uses a mathematical model based on fluid dynamics that integrates patient-specific imaging data with a population physiology model to solve the equations governing blood flow and calculate the blood flow velocity and pressure in the target vessel during simulated hyperemia. Software programs have been developed that can solve the Navier-Stokes equation and simulate patient-specific arterial models, and these have been applied to FFR-CT of the coronary arteries.[574,575] For example, the HeartFlow FFR-CT method involves acquisition of CCTA data, assessment of image quality, and use of an image segmentation algorithm to extract 3-dimensional models of the proximal aorta and coronary arteries. Next, the left ventricular myocardial volume is calculated to assess overall coronary blood flow demand, after which physiological models of aortic pressure and microcirculatory resistance are created in the order of the resting state followed by maximal hyperemia. Finally, the blood flow and pressure under simulated maximal hyperemia are

calculated for a patient-specific model, and the FFR-CT value (the ratio of mean coronary pressure to mean aortic pressure) is calculated from the pressure field using fluid dynamics.[576]

## 13.3 Importance of CCTA Imaging Protocol and Image Quality

Because FFR-CT analysis is used to predict the standard invasive FFR, it is necessary to administer nitrates to minimize the difference in vessel diameter between CCTA and cardiac catheterization. It is also important to optimize the imaging protocol to achieve adequate spatiotemporal resolution, and to calculate the luminal diameter by fine image segmentation despite the presence of calcification, motion, and other artifacts.

FFR-CT analysis uses standard CCTA data, so it is crucial to adhere to the SCCT guidelines on CCTA imaging[486] in order to obtain high-quality images that are suitable for 3D reconstruction and quantitative analysis. It is ideal to use a $\beta$-blocker to reduce the heart rate and perform imaging at a heart rate of <60 beats/min. It is also desirable to perform reconstruction of images by limiting the field of view to the heart, using a spatial resolution of ≥0.4–0.5 mm, and having a slice thickness of <1 mm.[486]

The spatial resolution of standard CCTA is generally sufficient to provide an anatomical model for FFR-CT analysis. However, poor image quality may interfere with interpretation of CCTA data and compromise the segmentation required for FFR-CT modeling (misalignment artifacts). A secondary analysis of the DeFACTO study (described later) demonstrated that administration of $\beta$-blockers and sublingual nitroglycerin within 30 min before imaging improved the specificity of FFR-CT (66.0% with a $\beta$-blocker vs. 51.0% without a $\beta$-blocker, P=0.03; 75.0% with nitroglycerin vs. 54.0% without nitroglycerin, P=0.013). The presence of misalignment artifacts decreased sensitivity from 86.0% to 43.0% (P=0.001), but the presence/absence of motion artifacts and the extent of coronary artery calcification did not influence diagnostic performance.[577]

## 13.4 Reproducibility

A secondary analysis of the NXT study (described later) examined the reproducibility of FFR-CT and standard FFR analysis in 28 patients (58 lesions) who twice underwent invasive measurement. FFR-CT measurements were performed by 2 independent analysts in a blinded manner at 2 different time points using the same CCTA dataset. For 12 lesions that showed an FFR ≤0.8, the coefficient of variation between the first and second FFR-CT measurements (interval: 51±11 days) was 3.4% (95% CI: 1.4–4.6), and the coefficient of variation between the first and second invasive FFR measurements (interval: 29±8 days) was 2.7% (95% CI: 1.8–3.3). Even for the lesions with FFR values in the range of 0.70–0.90, the coefficient of variation for FFR-CT and FFR was 3.3% (95% CI: 1.5–4.3) and 3.6% (95% CI: 2.3–4.6), respectively, indicating high reproducibility of both methods.[578]

## 13.5 Diagnostic Performance

The DISCOVER-FLOW study compared the performance of CCTA+FFR-CT (cutoff value: 0.8) with that of CCTA alone for diagnosis of ≥50% stenosis in 159 vessel segments of 103 patients (at 4 centers in 3 countries) who had known or suspected coronary heart disease and underwent CCTA/invasive coronary angiography/standard invasive FFR measurement, using the result obtained by invasive FFR (cutoff value: 0.8) as the reference. For FFR-CT vs. CCTA, the respective diagnostic accuracy was 84.3% and 58.5%, sensitivity was 87.9% and 91.4%, specificity was 82.2% and 39.6%, positive predictive value was 73.9% and 46.5%, and negative predictive value was 92.2% and 88.9%. Based on the area under the curve (AUC) determined by receiver-operator characteristics (ROC) analysis, diagnostic performance was significantly better with FFR-CT than CCTA (0.90 vs. 0.75, P=0.001). Although FFR-CT displayed slight underestimation (0.022±0.116, P=0.016), there was a strong correlation between FFR-CT values and invasive FFR values (r=0.717, P<0.001).[579]

Secondary analysis was performed in 42 patients (66 lesions) in whom the CACS (AS) was measured, including 11 patients with an AS of 101–400 and 13 patients with an AS ≥400. When the patients were divided into 3 groups based on the AS (0–100, 101–400, and ≥400), the diagnostic accuracy per patient was respectively 82.5%/95.0%/100%; and that per coronary artery was 77.8%/100%/100%. Accordingly, FFR-CT was beneficial for diagnosing stenosis associated with severe calcification.[580]

The DeFACTO study[581] prospectively evaluated the diagnostic performance of FFR-CT in 252 patients with stable angina enrolled at 17 centers in 5 countries who underwent invasive coronary angiography (including invasive FFR for 3 vessels) within 60 days of CCTA (≥64-row), investigating the hypothesis that the addition of FFR-CT to CCTA would improve the diagnostic performance for detecting significant stenosis (≥50%). The results showed a significant reduction of invasive FFR (cutoff value: 0.8) in 137 patients, and the sensitivity, specificity, and positive predictive value of CCTA+FFR-CT (cutoff value: 0.8) relative to invasive FFR (cutoff value: 0.8) was 90%, 54%, and 67%, respectively. However, the diagnostic accuracy of CCTA+FFR-CT was only 73% (95% CI: 67–78%) and the lower limit of the 95% CI did not exceed 70%, which was an unexpected result because the diagnostic accuracy of CCTA alone was 64% (95% CI: 58–70%).[582]

Using updated FFR-CT analysis software based on data from these 2 studies, the NXT study[583] compared CCTA+FFR-CT (cutoff value: 0.8) and CCTA alone for detecting ≥50% stenosis, with standard invasive FFR (cutoff value: 0.8) as the reference, in 254 patients who had 30–90% stenosis on CCTA and were enrolled at 10 centers in 9 countries, including Japan. Reproducibility of CCTA+FFR-CT (described above) was also evaluated and secondary analysis of patients with severe coronary artery calcification was performed. The per-patient diagnostic accuracy of CCTA+FFR-CT and CCTA alone was 81% and 53%; the sensitivity was 86% and 94%, specificity was 79% and 34%; positive predictive value was 65% and 40%; and negative predictive value was 93% and 92%, respectively. The AUC of the ROC analysis curve was 0.9 (95% CI: 0.87–0.94) and 0.81 (95% CI: 0.76–0.87), respectively, and the diagnostic performance of CCTA+FFR-CT was significantly higher (P=0.0008).[560]

In a secondary analysis, 214 patients who had their AS evaluated were divided into quartiles (by patient: 302±468 [0–3,599]; by coronary artery: 95±172 [0–1,703]), and it was found that the diagnostic accuracy, sensitivity, and

specificity of FFR-CT did not differ among the quartiles in both "per-patient" and "per coronary artery" analyses, with the diagnostic accuracy and specificity of FFR-CT being superior to those of CCTA alone. In the "per-patient" evaluation, when patients were divided into a high AS group (Q4: AS=416–3,599) and a low/intermediate AS group (Q1–Q3: AS=0–415), the AUC of the ROC analysis curve did not differ significantly between groups (AUC: 0.86 vs. 0.92; P=0.45). Similarly in the "per coronary artery" evaluation, the AUC of the ROC analysis curve for the high AS group (Q4: AS=121–1,703) and the low/intermediate AS group (Q1–Q3: AS=0–120) showed no significant difference (AUC: 0.91 vs. 0.95; P=0.65). In the high AS group, FFR-CT was superior to CCTA alone for diagnosing ischemia on a "per coronary artery" basis (AUC: 0.91 vs. 0.71; P=0.004), but no significant difference was noted on a "per-patient" basis (AUC: 0.86 vs. 0.72, P=0.09).[584] Post-hoc analysis of 57 Japanese patients enrolled in that study was also performed, revealing that CCTA+FFR-CT had significantly higher diagnostic accuracy than CCTA alone (74% vs. 47%, P<0.001). In addition, analysis of 47 Japanese patients (after excluding those with an AS >1,000, indicating severe calcification) showed a diagnostic accuracy of 83% and specificity of 76% for CCTA+FFR-CT, which were comparable to the results from the main NXT study (**Figure 12**).[573]

## 13.6 Impact on Diagnosis, Treatment Planning, Cost, and Quality of Life

Douglas et al investigated whether FFR-CT was useful for selecting patients who required invasive coronary angiography (PLATFORM study).[585] Patients with an intermediate level of risk who had new onset chest pain were enrolled prospectively, and patients in the first cohort (Cohort 1) were divided into those scheduled for noninvasive diagnostic procedures (CCTA, stress ECG, stress echocardiography, SPECT or MRI) (Group 1A) and those scheduled for invasive coronary angiography (Group 1B) according to routine clinical practice. After testing was done, the patients were treated according to the results and followed for 1 year. Enrollment of patients in the next cohort (Cohort 2) was carried out after completing enrollment in Cohort 1. The patients in Cohort 2 were divided into those scheduled for noninvasive diagnostic procedures (Group 2A) and those scheduled for invasive coronary angiography (Group 2B) according to routine practice. CCTA was also performed, which was not necessarily planned for all patients, and FFR-CT (cutoff value: 0.80) was added for lesions with ≥30% stenosis in vessels with a diameter ≥2 mm. Treatment was based on the results of CCTA+FFR-CT and follow-up was performed for 1 year.

Group 1B (n=187) and Group 2B (n=193) were scheduled for invasive coronary angiography, which revealed that 137 patients (73%) and 24 patients (12%), respectively, did not have occlusive coronary lesions. The difference in the frequency of unnecessary procedures between the 2 groups was 61% (95% CI: 53–69, P<0.0001). That is, 61% of the invasive coronary angiography procedures done in Group 1B could be avoided by performing FFR-CT. The average cumulative radiation exposure was 9.4±4.9 mSv in Group 1B and 9.9±8.7 mSv in Group 2B, so it was similar (P=0.20). Group 1A (n=100) and Group 2A (n=104) were initially scheduled for noninvasive examinations. The number of patients without occlusive coronary artery lesions on subsequent invasive coronary angiography was 6 (6%) and 13 (13%), respectively, showing no significant difference between these 2 groups (P=0.95). These findings indicate that FFR-CT is safe and effective for selecting patients who require invasive coronary angiography, and also that if FFR-CT is normal, it is highly likely invasive coronary angiography will not detect any obstructive lesions.[586]

In a secondary analysis of the cost-effectiveness and impact on QOL, assessment of the patients scheduled for invasive coronary angiography showed 32% of average cost reduction (for diagnostic tests, invasive procedures, hospitalization, and medications during 90 days of follow-up) in Group 2B (CCTA+FFR-CT) compared with Group 1B (standard management) (Group 1B: 10,734 USD vs. Group 2B: 7,343 USD; P<0.0001), but the difference in cost was not significant among the patients scheduled for noninvasive examination (Group 1A: 2,137 USD vs. Group 2A: 2,679 USD; P=0.26). QOL improved in all groups, and among the patients scheduled for noninvasive examination, there was a trend towards better QOL in the CCTA+FFR-CT group (Group 2A) compared with the standard management group (Group 1A).[587]

After follow-up for 1 year (n=581), MACE occurred in 4 patients scheduled for invasive coronary angiography (2 each in Groups 1B and 2B), while only 1 patient had a major cardiovascular event among those scheduled for noninvasive examination (standard management: Group 1A). Among patients scheduled for invasive coronary angiography, the total cost was significantly lower in Group 2B (CCTA+FFR-CT) than in Group 1B (standard management) (Group 1B: 12,145 USD vs. Group 2B: 8,127 USD; P<0.0001). Among patients scheduled for noninvasive examination, there was no significant difference in the total cost between Group 2A (CCTA+FFR-CT) and Group 1A (standard management) (Group 1A: 2,579 USD vs. Group 2A: 3,049 USD; P=0.82) if the cost of FFR-CT was assumed to be zero, but the total cost was significantly higher in Group 2A (3,223 USD) when the cost was assumed to be equivalent to that of CCTA (P<0.01). QOL showed similar improvement in both the patients undergoing CCTA+FFR-CT and those receiving standard management. Among patients scheduled for noninvasive examination, however, the 5-item EuroQOL scale score showed greater improvement in those receiving CCTA+FFR-CT than in those receiving standard management (mean change: 0.12 vs. 0.07, P=0.02).[588]

Outside the USA, the National Institute for Health and Care Excellence (NICE) of the UK reported in February 2017 that FFR-CT is safe and has a high diagnostic performance, and its use helps to avoid invasive testing. It was also stated that £214 could be saved per patient.[589] In Japan, assuming that the medical expenses of all 254 patients in the NXT study were covered by the Japanese healthcare system, costs would be lower for the patients undergoing CCTA+FFR-CT compared with those receiving standard management (7,222 USD equivalent vs. 10,360 USD equivalent) at 1 year, with a lower incidence of cardiac events (1.9% vs. 2.4%).[590]

## 13.7 Current Situation in Japan

In Japan, HeartFlow FFR-CT was covered by the national health insurance scheme in December 2018, but only a limited number of centers are eligible.[591]

**Table 36. Recommendations and Levels of Evidence for FFR-CT**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Angina patients with more than a moderate degree of coronary stenosis on cardiac CT; patients whose overall definitive diagnosis for myocardial ischemia is difficult; moreover, patients who are candidates for revascularization once myocardial ischemia is detected | IIb | B | B | II |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

(1) Patients who have undergone cardiac CT for medical reasons.
(2) Patients with stable symptoms.
(3) Patients with ≥50% stenosis on visual inspection of cardiac CT images in whom it is difficult to determine the presence or absence of myocardial ischemia from cardiac CT data and symptoms alone.
(4) Patients or lesions for which revascularization (PCI or CABG) is indicated if ischemia is detected.

On the other hand, the exclusion criteria almost match the criteria in the abovementioned representative studies of FFR-CT, such as DISCOVER-FLOW, DeFACTO, and NXT. For example, a history of PCI and CABG is also mentioned. CABG is still in the pilot stage[576] and is not indicated. As for PCI, a small study of 44 patients showed that simulation of PCI using FFR-CT was useful for predicting improvement of blood flow after stent placement,[592] albeit further studies are necessary.

## 13.8 Future Prospects

This section has primarily described the current status of HeartFlow FFR-CT, for which regulatory approval has been granted. Currently (as of December 2018), the ADVANCE study is underway with a target of 5,000 patients from around the world, and its primary endpoint is the extent to which CCTA+FFR-CT changes treatment strategies in comparison with CCTA alone.[593,594] In addition to HeartFlow FFR-CT, various attempts have been made to estimate the standard invasive FFR from CCTA data using different algorithms.[561–563] It would be extremely useful to be able to determine whether or not myocardial ischemia and revascularization are indicated by noninvasive CT. However, the clinical studies conducted so far have not allowed sufficient comparison with stress myocardial scintigraphy, the cornerstone of evaluation of myocardial ischemia. Further evidence is accordingly required. Recommendations and levels of evidence for FFR-CT are shown in **Table 36**.

# 14. Magnetic Resonance Imaging (MRI)

Cardiac MRI shows high diagnostic performance for evaluating myocardial infarction and myocardial ischemia, which are particularly important factors in the diagnosis and treatment of chronic coronary heart disease. LGE MRI clearly delineates the location and extent of myocardial infarction. It is useful for examining myocardial viability and for detecting right ventricular infarction,[595,596] as well as for detecting asymptomatic subendocardial infarction and small infarcts.[596] Stress myocardial perfusion MRI is useful for investigating the presence and extent of myocardial ischemia and can be used to clearly delineate subendocardial ischemia because of its high spatial resolution. Furthermore, a multicenter study and meta-analysis demonstrated better performance of stress myocardial perfusion MRI for diagnosing significant coronary stenosis compared with stress myocardial SPECT[597] There is also accumulating evidence about the usefulness of LGE MRI[598,599] and stress myocardial perfusion MRI[600–602] for predicting the prognosis of patients with coronary heart disease. The problems with cardiac MRI are the need for a long examination time when ≥2 imaging modalities are combined, and the possibility that sufficient image quality and diagnostic performance may not be achieved through inadequate knowledge and/or techniques for examination and imaging.

## 14.1 Characteristics and Technical Aspects

### 14.1.1 Advantages and Disadvantages

MRI is a diagnostic imaging method that involves the application of a strong magnetic field and measurement of changes in the alignment of protons in body water and fat. It is also characterized by no exposure to radiation. ECG-gated imaging of the heart is performed with breath-holding or with respiratory synchronization to minimize movement caused by the heart beating and respiratory excursion. Although the imaging time for cardiac MRI was initially quite long, innovations such as parallel imaging and compressed sensing have allowed high-speed imaging.[603] MRI has a higher spatial resolution than radionuclide imaging and has the advantage of being able to diagnose subendocardial infarction and subendocardial ischemia. Thanks to high contrast resolution between lesions and normal tissue, LGE MRI can delineate infarcted myocardium and fibrosis more clearly than contrast-enhanced CT. Because MRI is not affected by calcification or bone and there is no limitation of the visual field by the lungs, it is possible to obtain dynamic images in any desired cross-sectional view, and the reproducibility and objectivity of findings are also excellent.

The disadvantages of cardiac MRI are as follows. The scanner is more expensive than that for echocardiography, it cannot be performed at bedside, some imaging methods require a skilled technologist, and the imaging time is longer than for MDCT. Moreover, stress myocardial perfusion MRI requires pharmacological stress to be applied while the patient is in the MR unit, which is probably an obstacle to its widespread use.

With regard to the feasibility of undertaking cardiac MRI after implantation of various devices, the 2007 ACC/AHA guideline[604] indicates that it is safe to perform MRI at 1.5 or 3 T immediately after implantation of a DES, and there have been no reports of problems with other types of coronary stents. In addition, there have been no problems when MRI was performed postoperatively in patients with

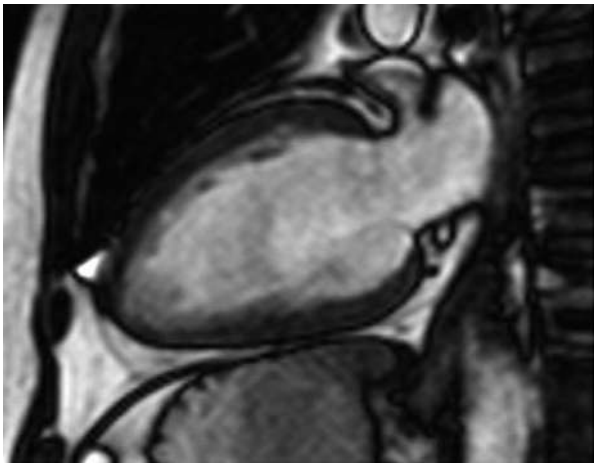


**Figure 13.** Cine MRI: vertical long axis view of the left ventricle. The left ventricular cavity shows high signal without use of contrast medium, providing a clear delineation of the border with the myocardium.

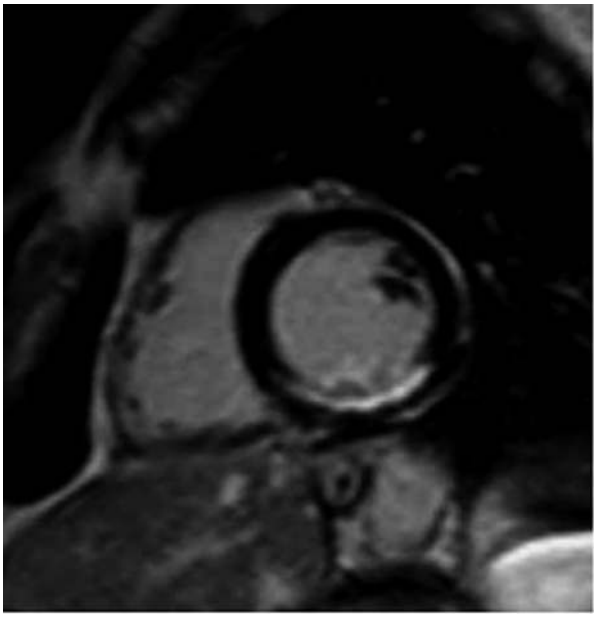


**Figure 14.** LGE MRI: short-axis view of the left ventricle. Subendocardial infarct tissue exhibits high signal intensity and provides an excellent contrast to non-infarct tissue with low signal intensity.

prosthetic heart valves. In relation to pacemakers and ICDs, an increasing number of devices are reported to be conditionally compatible with MR. However, adequate attention needs to be paid to device-specific standards and conditions for implementation of MRI.

### 14.1.2 Safety of Gadolinium-Based Contrast Media

Administration of a contrast agent is necessary for LGE MRI and stress myocardial perfusion MRI. NSF is a serious adverse reaction to gadolinium-based contrast media, in which pain, swelling, and hardening of the skin occur relatively acutely in patients with renal failure, particularly those on dialysis, and it can progress to cause contractures of the joints. In a gadolinium-based contrast medium, gadolinium is bound to a chelating agent. After intravenous administration, the contrast medium is filtered by the renal glomeruli and rapidly eliminated from the body if renal function is normal. However, the contrast medium remains in the body for an extended period in patients with renal failure, and it is thought that gadolinium is released from the chelator and deposited in the skin and other organs where it provokes fibrosis. Contrast agents for MRI are classified as linear or macrocyclic. The bond between gadolinium and the chelator is more stable in macrocyclic contrast agents than in linear agents, and NSF occurs more frequently when a linear contrast agent (with less stability) is administered to dialysis patients. As such, a macrocyclic contrast agent with high stability should be used when contrast-enhanced cardiac MRI is performed. The ESUR guidelines[605] recommend that patients with impaired renal function (stage 4–5 CKD) who require contrast-enhanced MRI should receive a minimum dose of a macrocyclic contrast agent (≤0.1 mmol/kg) and that the procedure should not be repeated within 7 days.[606,607]

## 14.2 Imaging Methods

### 14.2.1 Assessment of Cardiac Morphology and Function: Cine MRI (Figure 13)

Cine MRI is not influenced by bone or air, and can capture moving images of the heart with high spatial resolution in any desired projection. Precise measurement of left ventricular function can be performed, even in patients with myocardial infarction who have left ventricular deformity and abnormal wall motion. Cine MRI is currently the most accurate diagnostic procedure for assessment of cardiac function and regional wall motion.[608] In addition, measurement of left ventricular function and cardiac mass by MRI is highly reproducible and the results show minimal variation, so it is suitable for assessing changes over time and the response to treatment.[609,610] Recently, tracking-based analysis of cine MRI images from routine cardiac examination has enabled quantitative assessment of myocardial strain, and global strain determined from cine MRI is reported to be a better predictor of the prognosis after myocardial infarction than LVEF or infarct mass.[611]

### 14.2.2 Diagnosis of Myocardial Infarction: LGE MRI (Figure 14)

LGE MRI is currently the most accurate imaging modality for myocardial infarction. Imaging of LGE approximately 10 min after intravenous injection of a gadolinium-based contrast medium shows a high signal in infarcted myocardium from the acute to chronic phases, allowing the presence and extent of myocardial infarction to be examined. The advantages of LGE are that the contrast-enhanced area corresponds well with the pathological infarct zone on TTC (2,3,5-Triphenyl tetrazolium chloride) staining from the acute to the chronic phase,[612] and that its high spatial resolution allows examination of right ventricular infarction[595] and subendocardial infarction,[596] which cannot be assessed by radionuclide imaging. In an animal study based on histopathological comparison, the diagnostic sensitivity of LGE MRI for subendocardial infarction was 92%, which was higher than that of

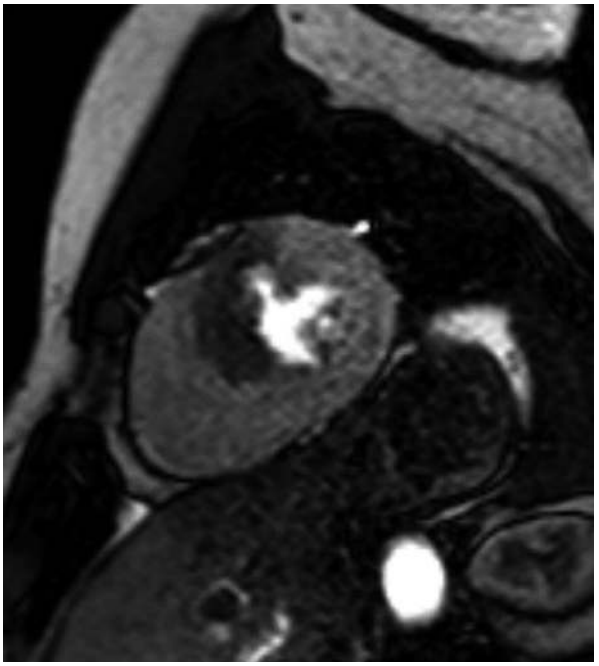


**Figure 15.** Stress myocardial perfusion MRI: short-axis view of the left ventricle. Myocardial ischemia in the anteroseptal wall associated with the left anterior descending artery stenosis is depicted as a region of low signal intensity during first-pass of contrast medium.

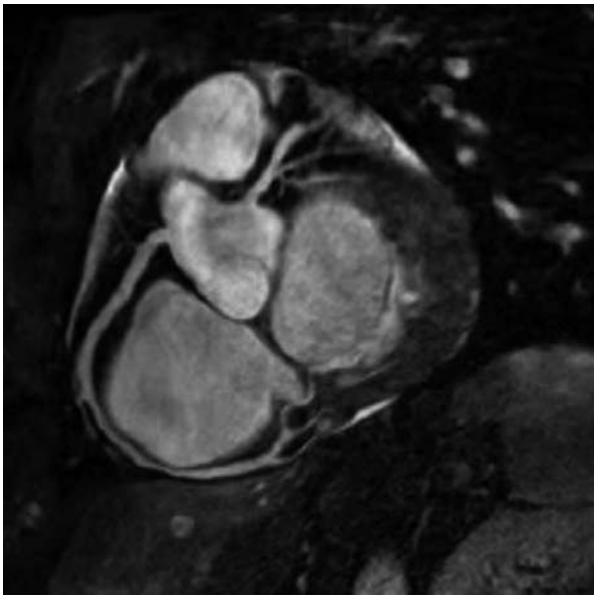


**Figure 16.** Whole-heart coronary MRA: maximum intensity projection image on the plane of the atrioventricular groove reveals the right coronary artery and proximal left coronary artery.

myocardial SPECT (28%).[612]

### 14.2.3 Diagnosis of Myocardial Ischemia: Stress Myocardial Perfusion MRI (Figure 15)

In patients with angina pectoris, the goal of performing revascularization for coronary stenosis is to eliminate myocardial ischemia. However, the morphological severity of stenosis on coronary angiography or CCTA does not always correspond with the extent of functional stenosis affecting blood flow. In order to improve prognosis by performing PCI, it is important to assess the presence or absence of myocardial ischemia and the extent of the ischemic region.[613] To perform myocardial perfusion MRI, bolus infusion of a gadolinium-based contrast medium is combined with dynamic MRI of the myocardium, allowing the myocardial blood flow distribution to be assessed from the first-pass myocardial dynamics of the contrast medium. A coronary vasodilator (e.g., adenosine, ATP, or dipyridamole) is administered to identify myocardial hypoperfusion associated with coronary artery stenosis. Because of its high spatial resolution, stress myocardial perfusion MRI can clearly depict subendocardial ischemia. Previous studies based on comparison with significant coronary artery stenosis detected by coronary angiography have indicated that stress myocardial perfusion MRI shows significantly better diagnostic performance than stress myocardial SPECT.[270,597,614]

### 14.2.4 Diagnosis of Coronary Artery Stenosis: Coronary MRA (Figure 16)

Some advantages of coronary MRA are not shared by CCTA, including absence of radiation exposure, no need for contrast agents, and no influence of severe coronary artery calcification. Whole-heart coronary MRA is a method for obtaining 3-dimensional images of the entire heart with respiratory synchronization and ECG gating.[615,616] Coronary MRA using a 1.5-T MRI unit is inferior to CCTA in terms of spatial resolution and imaging time, but coronary MRA is the method of first choice for patients with coronary artery anomalies, coronary artery aneurysm caused by Kawasaki disease, and renal failure.[617,618] In patients with severe coronary calcification, the specificity and negative predictive value of CCTA are compromised, whereas calcification has little influence on coronary MRA and diagnosis of stenosis is still possible. On the other hand, sites where metal stents have been implanted cannot be visualized, because of metal artifacts, so evaluation of stent restenosis cannot be performed with coronary MRA.

MRA is expected to be useful in screening for coronary heart disease because it does not involve radiation exposure and does not require the administration of contrast medium (noncontrast testing). There is no evidence for the usefulness of coronary MRA in asymptomatic patients, however. It should be noted that the positive predictive value of coronary MRA tends to be low in persons undergoing screening (who have a low pretest probability) and conversely many false-positive results may occur in such populations, leading to an increase in unnecessary CCTA and coronary angiography.

### 14.2.5 Blood Flow Measurement: Phase-Contrast Cine MRI

Phase-contrast cine MRI is used to measure blood flow by MRI. Phase-contrast cine MRI provides phase images in addition to conventional magnitude images, and the signals in the phase images are proportional to blood flow velocity. This method is sometimes used to measure blood flow in

the coronary arteries and bypass grafts for diagnosis of coronary heart disease.[619,620]

When phase-contrast cine MRI is used to measure coronary sinus blood flow at rest and after administration of a coronary vasodilator, the global blood flow reserve of the entire left ventricular myocardium can be determined noninvasively, which previously could not be evaluated without performing myocardial blood flow PET.[621] Recent reports from Western countries have indicated that reduction in global blood flow reserve on phase-contrast cine MRI is a prognostic factor that is independent of the presence and extent of ischemia and LGE, and it is highly useful for risk stratification of patients with coronary heart disease.[622,623]

## 14.3 Significance in the Diagnosis of Chronic Coronary Heart Disease

### 14.3.1 Evaluation of Myocardial Viability

LGE MRI can clearly delineate myocardial infarction from the acute to the chronic phase, and the transmural extent revealed by this modality strongly correlates with restoration of myocardial contractility. Accordingly, LGE MRI is useful for deciding treatment strategies, such as the indications for revascularization. Among cardiac segments with regional wall motion abnormalities, the rate of functional restoration after revascularization in patients with chronic coronary heart disease was 78% for segments with a transmural extent of 0%, decreasing to 60% for an extent of 1–25%, 42% for 26–50%, 10% for 51–75%, and 1.7% for 76–100%.[624] In addition, LGE MRI can clearly show whether or not myocardial necrosis exists in patents with hibernating or stunned myocardia, leading to better understanding of the pathological condition.

LGE MRI also provides high-resolution images that depict myocardial fibrosis and can accurately distinguish ischemic cardiomyopathy due to coronary heart disease from nonischemic cardiomyopathy on the basis of myocardial imaging patterns.[625] In ischemic cardiomyopathy, LGE involving the (sub-)endocardium and continuous in its epicardial direction is recognized. On the other hand, approximately 30% of patients with nonischemic cardiomyopathy show mid-wall LGE, which is closely associated with the risk of arrhythmic death.[626]

### 14.3.2 Diagnosis of Myocardial Ischemia

Stress myocardial perfusion MRI can identify regions of myocardial ischemia associated with coronary stenosis, and it is not only possible to diagnose coronary stenosis in patients with angina pectoris, but also to assess restenosis after PCI. MRI has better spatial resolution than radionuclide imaging and is superior for diagnosis of subendocardial ischemia and multivessel disease. Using significant stenosis on coronary angiography as the gold standard, research has indicated that stress myocardial perfusion MRI shows superior diagnostic performance to SPECT.[615] In a meta-analysis based on comparison with coronary angiography combined with FFR, the performance of stress myocardial perfusion MRI for detection of coronary artery lesions was significantly better than that of stress myocardial SPECT, and almost equivalent to stress myocardial perfusion PET.[627]

### 14.3.3 Prediction of the Prognosis

Evidence is being accumulated with regard to prediction of the prognosis by stress myocardial perfusion MRI and LGE MRI. A meta-analysis performed by Lipinski et al showed that the annual incidence of events (cardiac death or myocardial infarction) was 0.8±0.7% in patients who were negative for ischemia on stress myocardial perfusion MRI, but was 4.9±3.1% in those positive for ischemia and the odds ratio was 6.5 (95% confidence interval [CI]: 4.4–9.6).[628] In addition, the annual incidence of events was 1.4±1.0% in patients without infarction or fibrosis on LGE MRI and 4.6±4.0% in patients positive for late enhancement, with an odds ratio of 3.8 (95% CI: 2.6–5.7). Thus, the annual incidence of events is <1% in patients without ischemia on stress myocardial perfusion MRI, and stress cardiac MRI may have similar value to cardiac radionuclide imaging for risk stratification of patients with suspected coronary heart disease.

The CE-MARC study was a prospective comparison of diagnostic performance between cardiac MRI and myocardial SPECT, and it also compared the usefulness of these 2 modalities for predicting the risk of MACE.[629] Among the 628 patients who underwent both cardiac MRI and myocardial SPECT, 104 developed MACE, and univariate analysis showed that the hazard ratio for predicting MACE by cardiac MRI and myocardial SPECT was 2.77 ($P<0.001$) and 1.62 ($P=0.014$), respectively. Multivariate analysis showed that only cardiac MRI was a significant prognostic factor, and these results support the importance of selecting cardiac MRI for risk stratification of patients with suspected coronary heart disease.

Revascularization is known to improve prognosis more than medical therapy when stress myocardial SPECT shows that ischemic myocardium exceeds 10% of the total myocardial volume.[229] A recent study revealed that the ischemic myocardial volume threshold was 9% for performing revascularization based on stress myocardial perfusion MRI, and that patients with an ischemic myocardial volume <9% who did not undergo revascularization had a similar prognosis to those without ischemia.[630]

### 14.3.4 Coronary MRA

The greatest advantage of coronary MRA is that it can exclude the diagnosis of coronary stenosis in patients who have chronic coronary heart disease without exposing them to radiation. Disadvantages of coronary MRA include the longer imaging time, lower spatial resolution compared with CT, and difficulty in evaluating the lumen of coronary stents. In 2001, a multicenter study of gradient echo coronary MRA using catheter coronary angiography as the reference showed good sensitivity and specificity of MRA for left main trunk disease and triple-vessel disease. For lesions in the entire coronary artery tree, the sensitivity of MRA was high (93%), but its specificity was low (42%).[631] Coronary MRA imaging has since progressed to whole-heart coronary MRA using steady-state protocols,[632] and a multicenter Japanese study based on comparison with catheter coronary angiography showed improved diagnostic performance of MRA, with a sensitivity of 87%, specificity of 71%, positive predictive value of 71%, and negative predictive value of 87%.[633]

The 3-T MRI units provide images with a better signal-to-noise ratio than 1.5-T units, and allow acquisition of higher-quality coronary MRA images. A meta-analysis showed that 3 T coronary MRA has a sensitivity of 93% and specificity of 83%,[634] which means its diagnostic potential is approaching that of 64-row CT. Recent advances in

**Table 37. Recommendations and Levels of Evidence for MRI for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Cine MRI (chronic coronary syndrome with heart failure) | IIa | C | C1 | V |
| LGE MRI (differentiation between ischemic cardiomyopathy due to chronic coronary syndrome and nonischemic cardiomyocapathy) | IIa | B | B | IVa |
| LGE MRI (assessment of myocardial viability) | IIa | C | C1 | IVa |
| Stress myocardial perfusion MRI (assessing myocardial ischemia and evaluating indication of revascularization) | IIa | B | B | II |
| Coronary MRA (exclusion of coronary artery disease in the presence of chest pain syndrome) | IIb | C | C1 | IVb |
| MRA (screening of coronary artery disease in asymptomatic population) | III | C | C2 | VI |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

high-speed imaging techniques have made it possible to obtain coronary artery images that are adequate for daily clinical practice, with an imaging time of about 7 min.[635,636] Recommendations and levels of evidence for MRI are shown in **Table 37**.

### 14.4 Future Challenges

Of the various cardiac MRI methods, the usefulness of LGE MRI has been largely established, and it is widely used in daily practice together with cine MRI because there is little equipment-related variation in diagnostic performance and stress examination is unnecessary. In contrast, use of stress myocardial perfusion MRI is still limited compared with cine MRI or LGE MRI because it requires the patient to undergo pharmacological stress while in the MRI unit. In the future, it will be important to standardize the imaging methods and examination procedures for cardiac MRI, and to promote an objective method for assessing ischemia based on quantitative analysis of myocardial blood flow.

## 15. Coronary Angiography

Coronary angiography (CAG) can evaluate the presence, site, distribution, and extent (severity) of stenotic lesions or dilated lesions in the coronary arteries throughout the entire coronary artery tree. CAG is the best option for detailed assessment of coronary artery anatomy. Historically, CAG was initiated in 1958 with the invention of the so-called semiselective technique by Sones, in which a catheter was advanced to the left and right sinuses of Valsalva and 20–30 mL of contrast medium was injected over 3–6 s.[637] In 1967, a catheter with modified tip shapes for left and right CAG were developed by Judkins, and the percutaneous femoral approach was established.[638]

After that, the Sones approach via brachial arteriotomy and the Judkins approach with percutaneous femoral artery puncture were used for selective CAG, but today all catheterization is done via percutaneous puncture. CAG via minimally invasive radial artery puncture has become the mainstream method thanks to the availability of catheters with a smaller diameter. There has been remarkable progress in the imaging equipment; image quality has improved and radiation exposure has been minimized by the availability of digital flat panel detectors. Also, development of auto-injectors for contrast medium that are compatible with CASG has made it possible to obtain more stable images with a smaller volume of contrast medium.[639]

### 15.1 Indications

The indications for CAG should be determined by comprehensive evaluation of many factors, such as the patient's age, activities of daily living, comorbidities, and expectations. Accordingly, it is difficult to establish uniform criteria for the indications. However, it is generally considered appropriate to perform CAG in patients who have angina that interferes with daily activities or who are in the high risk (or sometimes moderate risk) category based on noninvasive tests, provided they are refractory to drug therapy. It is also considered reasonable to perform CAG in patients with atypical symptoms who require a definitive diagnosis if a stress test has failed to provide a diagnosis. Defining standard indications is important for preventing the overuse of CAG. One of the major reasons for performing CAG is to determine the indications for invasive therapies such as PCI and CABG. It is established that PCI or CABG improves angina pectoris, regardless of the number of vessels involved. It is thus important to distinguish patients with angina pectoris from asymptomatic persons. **Table 38** lists the main indications for CAG and related recommendations.[640,641]

### 15.2 Diagnostic Performance

CAG is the best choice for assessing the detailed anatomy of the coronary arteries, but it does not directly evaluate the functional severity of coronary artery lesions or associated physiological abnormalities. When performing CAG, the severity of stenosis is usually evaluated by comparison with a nearby contrast-enhanced "normal" vessel segment. However, the so-called normal vessel may be affected by arteriosclerosis, leading to underestimation of stenosis in many cases. Moreover, assessment of the absolute minimum vessel diameter does not help to define the extent of abnormality of the luminal diameter, because the appropriate

**Table 38. Recommendations and Levels of Evidence for Indication of Coronary Angiography for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Patients who have life-threatening ventricular arrhythmia or in those who have survived sudden cardiac arrest | I | B | B | IVa |
| Risk assessment in stable CAD patients with HF symptoms | I | B | A | III |
| Patients whose symptoms or results of noninvasive tests indicate high likelihood of severe CAD, if the benefits outweigh potential risks | I | C | A | IVa |
| Patients who receive evidence-based medical therapy, but have recurrence of angina | I | C | A | III |
| Assessment of severity of CAD in stable patients whose clinical characteristics and/or results of noninvasive tests indicate the presence of CAD | IIa | C | C1 | VI |
| Patients who can not undergo noninvasive tests or in those who have an inconclusive result for noninvasive tests | IIa | C | C1 | VI |
| Risk assessment in stable CAD patients with reduced LV function (LVEF ≤50%) and moderate-risk criteria on noninvasive tests | IIa | C | B | IVa |
| Determine the indication of coronary revascularization in HF patients with suspected CAD possibly related to developing HF | IIa | C | A | I |
| Patients who have impaired QOL due to angina, have preserved LV function (LVEF >50%) and moderate-risk criteria on noninvasive tests | IIa | C | B | II |
| Patients with strongly suspected CAD and negative results for appropriate noninvasive stress tests | IIb | C | C1 | VI |
| Risk assessment in stable CAD patients without indication of coronary revascularization | III | B | C2 | II |
| Patients with preserved LV function (LVEF >50%) and low risk criteria on noninvasive tests | III | B | D | II |
| Routine follow-up after PCI | III | A | D | I |
| Clinically low-risk patients who have not had an assessment by noninvasive tests | III | C | C2 | VI |
| Asymptomatic patients without evidence of ischemia on noninvasive tests | III | C | C2 | VI |
| Routine coronary angiography before noncardiac surgery | III | C | C2 | VI |
| Assess bypass graft patency after CABG in patients without ischemic symptoms or without results of noninvasive tests indicating ischemia | III | C | C2 | VI |

CAD, coronary artery disease; COR, class of recommendation; GOR, grade of recommendation; HF, heart failure; LOE, level of evidence; LV, left ventricular.

luminal diameter varies depending on the site of the lesion. It is also difficult to estimate the luminal area of a tortuous vessel. This problem is evident immediately after PCI.

Issues with reproducibility are also inevitable when evaluating coronary lesions, particularly when a visual assessment is performed. To overcome this limitation, several methods of quantitative CAG have been developed, including edge detection and video densitometry.[642] Although reproducibility and objectivity are markedly improved by quantitative CAG, accuracy is inferior at sites with a luminal diameter ≤1 mm because of problems with resolution. When assessing the functional significance of lesions, a range of about 1 mm in luminal diameter is of vital importance. CAG provides a view of the borders of the vessel lumen and does not provide information on the nature of the coronary artery wall or the severity of atheroma. To assess the properties of the coronary artery wall, the extent of atherosclerosis, and the true luminal diameter, imaging methods that can evaluate the vessel walls, such as coronary artery IVUS (described later), should be combined with angiography.[643]

## 15.3 Results and Their Significance

CAG is the best method for visually demonstrating the presence of coronary artery stenosis and coronary artery spasm, although it has limitations for diagnosis of coronary heart disease, as described in the previous section. Clarifying the presence of coronary heart disease can help to determine the need for coronary revascularization and drug therapy.

### 15.3.1 Assessment of Severity

Assessment of the severity of coronary heart disease is the most important use for CAG, because assessment of severity allows stratification of the vital prognosis. The prognostic factors that are currently known to be obtained from CAG and left ventriculography include ≥50% stenosis of the left main trunk, as well as the presence of triple-vessel disease with left heart dysfunction (LVEF <50%).[644] In patients with these findings, CABG has been shown to improve the vital prognosis. The SYNTAX score is an indicator of the complexity of coronary lesions on CAG, and it has been reported to be useful for selecting CABG or PCI for patients with severe coronary heart disease such as triple-vessel or

left main trunk disease.[645,646]

### 15.3.2 Determination of Indications for Treatment

Despite the fact that CCTA has provided new options for evaluation of coronary lesions, CAG is still essential for examining the anatomical suitability of a patient for invasive treatment (PCI or CABG). Information that can be obtained from CAG, such as the site of lesion, severity of stenosis, vessel diameter, lesion length, presence/absence of thrombus, and presence/absence of calcification, is important for predicting the initial success of PCI and long-term outcomes. The presence or absence of peripheral coronary artery lesions is also important to determine when deciding the indications for CABG.

### 15.3.3 Assessment of the Effect of Treatment

CAG is often performed to detect restenosis after PCI, to assess the patency of coronary artery bypass grafts, or to investigate regression of coronary lesions. Although QCA has played a significant role in clinical studies evaluating improvements of devices, it has often been pointed out that a clinical index should be used in such studies rather than an imaging index. In particular, the clinical significance of CAG for judging the effects of treatment has not been clarified. It has also been reported that performing follow-up CAG adds to the rate of repeat PCI.[647] Accordingly, routine follow-up CAG, which was conventionally performed after PCI, is not recommended for patients without symptoms or ischemic findings. Likewise, performing CAG after CABG to evaluate graft patency is not recommended in the absence of symptoms or ischemic findings.

### 15.4 Complications

The incidence of death associated with CAG does not exceed 0.2%, and the incidence of major complications (stroke, myocardial infarction, and hemorrhage) does not exceed 0.5%.[648] The risk of complications is higher when a decrease in blood pressure is noted on exercise testing or ST depression is widespread and prominent together with a low heart rate.[26] Other risk factors that have been identified include left main trunk disease, severe triple-vessel disease, left heart dysfunction, critical aortic stenosis, and advanced age.[649]

In recent years, the incidence of serious complications has been decreasing due to miniaturization of catheters, improvement of catheterization techniques, and better treatment of complications. For example, myocardial infarction caused by coronary artery dissection was generally a serious complication leading to emergency CABG and death, but it is now possible to avoid infarction by rapid deployment of a stent. In addition, CAG via radial artery puncture has been reported to result in approximately 70% fewer major bleeding complications and approximately 30% fewer major cardiovascular complications (death, myocardial infarction, and stroke) compared with femoral artery puncture.[650] Moreover, anaphylactic shock due to ionic contrast medium was not a rare event, but use of nonionic contrast media has dramatically reduced the incidence of shock. Although thrombus formation associated with nonionic contrast media has been pointed out in Western countries, it does not seem to be a major problem in Japanese patients.

It has also been pointed out that CAG can lead to performance of unnecessary PCI and CABG. This issue has long been known and has been given the name of the oculostenotic reflex, which means that nonindicated use of CAG leads to an increase in PCI and CABG procedures without obvious clinical value. Therefore, CAG should only be performed according to appropriate indications.

## 16. Coronary Spasm Provocation Testing

Coronary spasm provocation testing is performed by combining coronary artery imaging with selective intracoronary infusion of acetylcholine or ergonovine. It is done to confirm coronary spasm in patients with rest angina or to exclude coronary spasm in patients with atypical chest pain, and is also sometimes performed in patients with effort angina or nonacute myocardial infarction. The sensitivity and specificity of provocation testing for detection of coronary spasm are as high as 80–90%. Sensitivity is reduced by drug therapy before stress testing and is also lower in patients with less frequent attacks. It sometimes is difficult to determine whether coronary spasm induced by this test has true clinical and pathological significance. However, patients with multivessel coronary spasm have a poor long-term prognosis. With regard to coronary spasm testing with acetylcholine, an additional indication (Ovisot® for Injection 0.1 g) was approved on August 25, 2017, and health insurance cover was officially granted for pharmacological coronary spasm testing with acetylcholine in the 2018 fiscal year.

### 16.1 Characteristics and Technical Aspects

There are many patients with rest angina in Japan. In these patients, coronary angiography often confirms coronary spasm,[651,652] but the frequency of angina attacks is not necessarily high when Holter ECG is performed. For this reason, invasive coronary spasm provocation testing with acetylcholine or ergonovine is often performed in patients with rest angina.

Typically, an acetylcholine[653] or ergonovine provocation test[654] is implemented. In the acetylcholine provocation test, selective intracoronary infusion of acetylcholine is performed at a dose of 20–100 $\mu$g. The initial intracoronary dose is smaller (20 $\mu$g) in patients with frequent angina attacks who are considered to have highly active disease. Because hypotension and severe bradycardia may occur during a spontaneous attack, a temporary pacing electrode should be inserted into the right ventricle.

Regarding the ergonovine provocation test, there was an early report of death due to intravenous administration of a high dose of ergonovine,[655] but the usefulness of this test with intracoronary administration was subsequently reported. Thus, selective intracoronary administration, which requires lower doses of ergonovine, is now widely adopted.[656,657] The dose of ergonovine for intracoronary administration varies among institutions, and there is no generally accepted standard.[658] However, a dose of at least 20–60 $\mu$g for both the left and right coronary arteries is common. For safety reasons, bolus dosing should be avoided if possible and continuous infusion should be performed instead.

### 16.2 Criteria for Deciding the Indications

**Table 39** summarizes the criteria for deciding the indications for coronary spasm provocation testing with reference to

**Table 39. Recommendations and Levels of Evidence for Spasm Provocation Tests**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Patients in whom vasospastic angina is suspected based on symptoms, but who have not been diagnosed with coronary spasm by noninvasive evaluation | I | B | C1 | IVa |
| Patients who have been diagnosed with coronary spasm by noninvasive evaluation, and in whom medical treatment is ineffective or insufficiently effective | IIa | B | C1 | IVa |
| Patients who have been diagnosed with coronary spasm by noninvasive evaluation, and in whom medical treatment has been effective | IIb | B | C1 | IVa |
| Patients without symptoms suggestive of vasospastic angina | III | C | C2 | VI |
| Patients who are more likely to develop severe and potentially fatal complications of induced coronary spasm (left main trunk disease, multivessel disease including an occlusive lesion, severe cardiac dysfunction, untreated congestive heart failure, etc.) | III | C | C2 | VI |
| Patients with ACS undergoing emergency coronary angiography | III | C | C2 | VI |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence. (Reproduced from data in Ogawa et al,[63] with permission.)

the indication categories in the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina (Coronary Spastic Angina) of the Japanese Circulation Society.[63,659–664]

## 16.3 Significance in the Diagnosis of Chronic Coronary Heart Disease

### 16.3.1 Objectives of Testing

The objectives of performing a provocation test are: (1) confirmation of coronary spasm in patients with rest angina and some patients with effort angina; (2) determination of the severity of rest angina; and (3) exclusion of coronary spasm in patients with atypical chest pain.

### 16.3.2 Diagnostic Performance

The sensitivity and specificity of coronary spasm provocation testing is generally quite high, being in the range of 80–90%.[654,657,665–668] However, coronary spasm may not be provoked in patients who have received drug therapy before testing or in patients with infrequent spasm, even if ST elevation is confirmed by Holter ECG. Also, there are diurnal variations in the frequency of coronary spasm, and attacks only occur in the early morning in some patients.[666] Therefore, to increase the diagnostic accuracy of pharmacological coronary spasm provocation testing, it should be performed in the morning whenever possible, and drugs, such as calcium antagonists and long-acting nitrates, should be discontinued for at least 2 days before testing if possible. On the other hand, coronary spasm associated with ECG changes may be induced even in patients without history of chest pain, but the pathological significance of such spasm is difficult to judge. The pathological significance of coronary spasm without associated ECG changes and without complete or subtotal occlusion is also difficult to assess.

### 16.3.3 Results and Diagnostic Significance

Confirmation of coronary spasm in patients with rest angina and some patients with effort angina justifies long-term administration of nitrates and calcium antagonists as treatment for angina pectoris. It also provides information to guide treatment with other drugs, such as whether $\beta$-blockers (which can induce coronary spasm) should be administered. Regarding the severity of rest angina, patients with multivessel coronary spasm have a poor long-term prognosis.[667] An association between occult atherosclerotic lesions and prognosis has also been shown.[669] In such cases, the results of provocation testing may be used to guide decisions about drug doses and the duration of treatment.

Excluding coronary spasm in patients with atypical chest pain is crucial, especially in the Japanese population, because angina stemming from coronary spasm is more frequent in Japan.[670] CCTA has become popular in recent years and has a very high negative predictive value, so excluding coronary stenosis in patients with atypical chest pain is possible without catheter coronary angiography. However, absence of coronary stenosis does not directly exclude a diagnosis of angina. It is also problematic to keep patients on long-term treatment with nitrates or calcium antagonists for atypical chest pain without a definitive diagnosis of angina pectoris. It is crucial to perform coronary spasm provocation testing in patients with atypical chest pain to determine the appropriate therapeutic strategy.

## 16.4 Contraindications

Pharmacological coronary spasm provocation testing is invasive and extreme caution should be exercised when deciding the indications for this test. As indicated in **Table 39**, pharmacological coronary spasm provocation testing should not be performed in patients who are likely to be disadvantaged by undergoing such a test, including (1) patients without symptoms suggestive of vasospastic angina; (2) patients who are more likely to develop severe and potentially fatal complications of induced coronary spasm (left main trunk disease, multivessel disease including an occlusive lesion, severe cardiac dysfunction, untreated congestive heart failure, etc.); and (3) patients with ACS undergoing emergency coronary angiography.

## 16.5 Complications

When coronary spasm provocation testing is performed, severe and extensive coronary spasm may be induced and the induced vasospasm may be prolonged, especially in patients with frequent attacks or multivessel coronary

**Table 40. Performance Comparison: IVUS, FD-OCT and OFDI**

| | IVUS* | FD-OCT | OFDI |
|---|---|---|---|
| Resolution (axial) | ≤200 μm | 12–15 μm | <20 μm |
| Resolution (lateral) | ≤200 μm | 19 μm | <20 μm** |
| Frame rate | 30/60/90 (frames/s) | 180 frames/s | 158 frames/s |
| Pullback speed | 0.5/1.0/2.0 3.0/6.0/9.0 (mm/s) | 36 mm/s 18 mm/s | 40 mm/s |
| Scan diameter | 32 mm | 10 mm | 9–10 mm |

*TERUMO: Altaview™; **1.5 mm from center of imaging catheter.

spasm. As a result, hypotension, cardiogenic shock, severe arrhythmia, and cardiac arrest may occur. In such cases, immediate alleviation of coronary spasm by intracoronary infusion of a nitrate, administration of vasopressors to maintain the blood pressure, and immediate countermeasures for serious arrhythmia may be necessary. A recent investigation of complications in 17,700 patients undergoing coronary spasm provocation testing by intracoronary administration of acetylcholine or ergonovine showed that serious procedural complications had a frequency of 0.89%, including 1 death (0.006%) and 2 cases of acute myocardial infarction (0.01%).[671]

## 17. Intravascular Ultrasound and Optical Coherence Tomography

Coronary angiography is the gold standard for imaging diagnosis of coronary heart disease and it has long been used as the basis for deciding the indications for PCI and CABG, as well as for evaluation after treatment. However, coronary angiography only provides a 2-dimensional projection of the blood vessel lumen that is obtained by using contrast medium, which means that overlapping and longitudinal shortening of blood vessels are unavoidable, resulting in inaccurate evaluation of bifurcation lesions. It is also difficult to evaluate the distribution and properties of atheromatous plaque on the coronary artery walls.[643] On the other hand, IVUS and OCT are intravascular imaging techniques in which a catheter with a diameter of ≈1 mm is inserted into the target coronary artery and cross-sectional images of the vessel are obtained using ultrasound or near-infrared light. These methods allow more precise measurement of vessel dimensions and detailed morphological assessment of coronary plaques.

### 17.1 Characteristics of Intravascular Imaging

#### 17.1.1 IVUS

When IVUS is performed, ultrasound is emitted from a transducer located at the tip of the IVUS catheter, and the ultrasound waves reflected from the coronary artery wall are converted into electrical signals that provide images of the cross-sectional architecture of the vessel. IVUS can be performed by mechanical or electronic scanning. With mechanical scanning, a single transducer rotates in the catheter at high speed to construct a 360-degree image. With electronic scanning, multiple ultrasonic transducers are arranged around the circumference of the catheter tip, and ultrasound waves are generated by each transducer to provide a 360-degree image. Generally, mechanical scanning uses high-frequency ultrasound (40–60 MHz) and achieves high resolution, but images of tortuous vessels may be skewed because of non-uniform rotational distortion (NURD) as the probe rotates inside the catheter. In contrast, NURD does not occur in tortuous vessels with electronic scanning because there is no rotating transducer, but the frequency of the ultrasound waves is only ≈20 MHz and resolution is inferior. When performing IVUS by either method, the catheter is advanced until the sensor crosses the lesion, and then motorized pull back is performed at a constant speed (0.5–1.0 mm/s) to obtain cross-sectional images of the vessel.

Recently, IVUS catheters that allow high-speed pullback (9.0 mm/s) and still achieve excellent resolution using high-frequency ultrasound (60 MHz) and increasing the frame rate have become more popular.[672] IVUS generally has the advantage of achieving transmural penetration, which makes it suitable for evaluation of the entire coronary artery wall, although its resolution is inferior to that of OCT (described next).

#### 17.1.2 OCT

OCT is a relatively new intravascular imaging method that uses near-infrared light at a wavelength of ≈1,300 nm and constructs cross-sectional images of a coronary artery by analysis of the interference between light reflected from the artery and light reflected from a mirror in the equipment. Currently, 2 types of OCT are available for clinical use: frequency domain OCT (FD-OCT; Abbott) and optical frequency domain imaging (OFDI; Terumo).[673] With both types, depth information can be obtained instantaneously by rapidly changing the frequency of the near-infrared band, so the spatial resolution is extremely high and the imaging time is short, enabling more rapid pullback compared with IVUS. **Table 40** compares the performance of IVUS, FD-OCT, and OFDI. Because the near-infrared light used in OCT is attenuated by red blood cells in the artery, imaging is performed over several seconds after a contrast agent or low-molecular-weight dextran is injected through a guiding catheter to temporarily block coronary blood flow.

### 17.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

#### 17.2.1 IVUS

The coronary artery wall has a 3-layer structure, consisting of the tunica intima, tunica media, and tunica adventitia in order from the lumen. IVUS cannot visualize the normal tunica intima, but can depict plaques in atherosclerotic lesions as local thickening of the intima. In actual observation, the boundary between the intima and the media is often unclear and the cross-sectional area of a plaque is defined as the area of the IMC, which is calculated by tracing of the media–adventitia boundary and subtracting the luminal area (intimal area + medial area). The cross-sectional area of the lumen at the site of maximal stenosis is called the minimum lumen area. Coronary plaques are classified as soft or hard according to the IVUS echo level, but the correlation of this classification with actual plaque hardness or tissue characteristics is not strong. Recently, it has become possible to predict coronary artery tissue characteristics by displaying different tissues in different

colors on IVUS images using various algorithms to compare ultrasound signals with pathological data, which is known as virtual histology IVUS (VH-IVUS: Volcano), integrated backscatter IVUS (IB-IVUS: Terumo), or iMAP (Boston Scientific).[674]

Calcified lesions are characterized by high echo levels and acoustic shadowing, which allows identification with high sensitivity and specificity (≥90%). Plaques with attenuation despite the absence of calcification are called attenuated plaques, and are considered to be lesions associated with a higher risk of no reflow/slow flow after PCI.[675,676] Recently, IVUS has been combined with a system that detects cholesterol ester-rich lipid core plaque by near-infrared spectroscopy (NIRS-IVUS, Infraredx) and this method has been applied clinically.[677] If basing therapeutic strategy on tissue characterization is shown to improve the prognosis, IVUS will be increasingly used in the future.

IVUS is also useful for determining the required size and length of coronary stents before implantation. When sizing a vessel to select balloons and stents, it is important to take vascular remodeling into account, in addition to the actual coronary artery lumen. Conventionally, the outer diameter of the distal reference vessel (media–adventitia boundary) is measured by IVUS and multiplied by 0.8–0.9 to obtain the size of the stent or balloon. Use of DES with less late lumen loss has become mainstream practice, and the stent diameter is often determined from the lumen diameter. However, care is required when the lesion is associated with negative remodeling, because there is a risk of perforation if only the reference vessel diameter is used for guidance. IVUS can also provide useful information for determining stent length by assessing residual plaque proximal to the lesion and plaque in distal segments, as well as for predicting and detecting complications such as hematoma and perforation.

A number of observational studies, meta-analyses, and RCTs have recently demonstrated the clinical usefulness of IVUS-guided PCI.[678,679] In particular, IVUS-guided PCI has been shown to be useful for patients with long lesions[680] or chronic total occlusion.[681] A meta-analysis focusing on RCTs also suggested that IVUS-guided PCI significantly reduces major cardiovascular events, particularly target vessel revascularization, compared with reliance on coronary angiography alone.[682]

### 17.2.2 OCT

In OCT, the coronary artery wall is clearly observed as a layered structure, with the tunica intima showing high brightness, while the tunica media shows low brightness and the tunica adventitia also shows high brightness. In addition, coronary artery plaques have specific characteristics. Fibrous plaques are depicted as regions of high intensity with indistinct boundaries. Lipid plaques are low intensity areas with diffuse borders, while calcified plaques are seen as low brightness areas with clear borders. OCT can also identify the contours of calcification, allowing for quantitative assessment of superficial calcified lesions.[683] The diagnostic sensitivity and specificity of OCT for lipid plaques were reported to be 90–94% and 90–92%, respectively, with respective values of 95–96% and 97% for calcified plaques and 71–79% and 97–98% for fibrous plaques.[684] Pathological studies have shown that progression of atherosclerosis leads to development of TCFA containing a pool of lipids and cholesterol crystals, with disruption of the TCFA thought to be the main underlying cause of ACS. On OCT, TCFA is defined by detection of a thin fibrous capsule (≤65 $\mu$m) with a necrotic core occupying ≥1/4 of the vessel's circumference.[685] It was reported that examination of culprit lesions of ACS by OCT showed disruption of TCFA (plaque rupture) in 43.7%, plaque erosion in 31.0%, and calcified nodules in 7.9%.[686]

When performing OCT-guided PCI, the diameter of the stent is determined from the distal reference lumen diameter and a stent 0.25–0.5 mm larger than the measured lumen diameter is often selected. Recently, it has been suggested that the stent size should be determined based on the outer border of the tunica media (external elastic lamina), in light of the results of the ILUMIEN III study (described below). It has also been reported that incomplete stent expansion and chronic in-stent restenosis are associated with the severity of calcification assessed by OCT at the time of PCI, as well as with the presence or absence of cracking at sites of calcification after balloon dilatation.[687,688] Moreover, detection of TCFA by OCT is associated with an increased risk of no reflow/slow flow after PCI (PCI-related myocardial infarction: type 4).[689,690] Thus, OCT provides useful information for optimal stenting.

Both 2-dimensional long-axis images and 3-dimensional images can be obtained by OCT. Three-dimensional imaging allows visual observation of the complex architecture of the coronary arteries and the positional relations of guidewires and other devices, and its use as a guide for PCI is increasing, especially in the treatment of bifurcation lesions.

A recent retrospective comparison of OCT-guided PCI and coronary angiography alone showed significantly lower 12-month rates of cardiac death and myocardial infarction with OCT guidance.[691] The influence of OCT on selection of PCI procedures was investigated in a multicenter prospective study (ILUMIEN I), revealing that the treatment strategy was changed in 57% of patients and additional measures to optimize treatment were carried out in 27%.[692] A recent multicenter randomized controlled study (ILUMIEN III) showed that OCT guidance achieved

**Table 41. Recommendations and Levels of Evidence for Use of IVUS and OCT for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| IVUS is reasonable for assessing severity and optimizing treatment of left main coronary artery disease | IIa | B | B | III |
| IVUS or OCT is reasonable for assessing mechanisms of stent failure | IIa | C | B | IVb |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

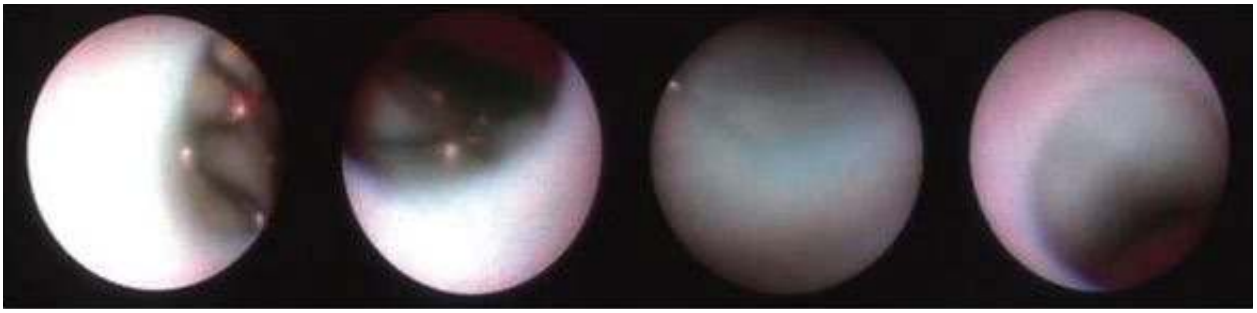



**Figure 17.** Neointimal grades of angioscopy after stent implantation. Grade 0: stent struts are clearly visible. Grade 1: stent struts are thinly covered with neointima, but the stent is visible. Grade 2: stent struts are almost covered with neointima, but the stent is slightly transparent. Grade 3: stent struts are fully covered with neointima and the stent can not be visible. (Reproduced from Takayama et al 2011,[704] with permission.)

similar stent expansion to IVUS, with no significant difference in major cardiovascular events up to 30 days after PCI.[693]

A Japanese multicenter randomized trial (OPINION study) compared the outcome and prognosis of OCT-guided PCI with IVUS-guided PCI, revealing no significant difference in target vessel failure (target vessel-related death, myocardial infarction, or revascularization for ischemia) and demonstrating noninferiority of OCT-guided PCI to IVUS-guided PCI (P=0.042 for noninferiority).[694] Although there is not yet as much evidence for OCT-guided PCI as for IVUS-guided PCI, increasing use of OCT with its high resolution in the diagnosis and treatment of coronary heart disease is expected in the future. Recommendations and levels of evidence for IVUS and OCT are shown in **Table 41**.

### 17.3 Future Challenges

In patients with complex lesions, combining PCI with intravascular imaging has been shown to not only improve the acute outcome but also the long-term prognosis compared with PCI based on coronary angiography alone. On the other hand, assessment of coronary artery lesions, decisions about the indications for PCI, and treatment strategies vary widely among patients. It is important to select the optimum strategy by comprehensively assessing the clinical background, the results of coronary angiography, and the findings on intravascular imaging.

## 18. Angioscopy

### 18.1 Characteristics

Angioscopy is the only procedure by which the interior of a blood vessel can be viewed directly in vivo.[695] The angioscope is very thin (0.75 mm in diameter) and can be safely inserted into the coronary arteries, allowing the status of plaque in the arteries to be observed directly. Plaque is localized intimal thickening of a blood vessel due to arteriosclerosis. Angioscopy provides a "true image," allowing observation of the color and surface of plaques, as well as the presence of thrombus. Angioscopy is superior for detecting thrombi and yellow plaques, particularly in patients with ACS,[696–698] as well as for assessing stents after placement. This technology was developed in Japan and evidence has been accumulated for Japanese patients, albeit little information has been obtained in other countries.

#### 18.1.1 Yellow Plaque

Formation of a yellow plaque starts with deposition of lipids in the coronary artery wall. The deposits form a lipid core that increases in size over time. As the fibrous capsule covering the lipid core becomes thinner, the surface of the plaque develops a yellowish color. The yellowness of plaques can be graded by angioscopy (grade 0: white; grade 1: light yellow; grade 2: yellow; grade 3: dark yellow), and the yellow grade closely correlates with the thickness of the fibrous capsule in vivo.[685,699] A higher yellow grade indicates more vulnerable plaque that is more likely to cause ACS.

It has been demonstrated that reduction of the LDL-cholesterol level with statin therapy decreases the yellow grade and stabilizes plaques.[700] It has also been shown by angioscopy that not all ruptured plaque causes ACS, and that asymptomatic plaque rupture can occur. The features of plaque rupture include intimal fissures, erosions, and ulceration. Angioscopy is also important for assessing the anti-atherosclerotic effect of cholesterol-lowering drugs such as statins.[700–702]

#### 18.1.2 Thrombus

Angioscopy can detect even small thrombi and is superior to IVUS or OCT in this regard.[695] Thrombus can be classified as white thrombus (considered to be platelet-fibrin thrombus), red thrombus (mainly contains erythrocytes), and mixed thrombus (a mixture of white and red thrombus).[696–698]

#### 18.1.3 Neointima After Stent Implantation

After stenting in patients with both ACS and stable angina, angioscopy is useful for investigating whether the stent is covered by neointima in the chronic phase and whether it is free of thrombus etc. If the metal parts of the stent are completely covered by neointima and no thrombus is present, reducing the dosage or ceasing antiplatelet drugs can be considered.[703]

The extent of neointimal coverage of stents is classified

**Table 42. Recommendations and Levels of Evidence for Angioscopy**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Angioscopy at follow-up CAG after stent implantation | IIb | B | C1 | III |
| Detection of vulnerable plaque at follow-up CAG | IIa | B | C1 | III |

CAG, coronary angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

into 4 grades (0–3) (**Figure 17**).[704]

Poor neointimal coverage and thrombi are common at sites of contrast medium exudation outside the stent (peri-stent contrast staining [PSS]), which is associated with very late stent thrombosis (VLST), a problem with 1st-generation DES.[705,706] The 2nd-generation DES show better neointimal coverage compared with 1st-generation DES.[707] With 3rd-generation DES, the occurrence of thrombosis has been reduced by the thinner stent struts and other changes.[708]

Yellow plaque at the site of a stent is associated with cardiac death, ACS, and target lesion revascularization at 1 year, whereas reduction of LDL-cholesterol with statin therapy is associated with risk reduction.[709] Thus, angioscopic assessment of the intimal coverage of stents can often provide helpful findings for early discontinuation of dual-antiplatelet therapy and for management of lipid-lowering therapy. Recommendations and evidence levels for angioscopy are shown in **Table 42**.

## 19. Measurement of Intracoronary Pressure and FFR

### 19.1 Characteristics and Technical Aspects

Coronary angiography is regarded as the standard examination for diagnosis of chronic coronary heart disease, and the angiographic severity of stenosis has been used to determine the severity of this condition and the indications for revascularization. However, anatomical information obtained from coronary angiography cannot provide accurate information on the functional severity of a stenosis.[710]

FFR is a parameter that assesses the functional severity of coronary stenosis and can be measured during coronary angiography, and it can be used to precisely assess the hemodynamic severity of stenotic lesions. FFR is determined by measuring the intracoronary pressure using a pressure guidewire. Coronary blood flow can be estimated by intracoronary pressure, because blood primarily perfuses the myocardium during diastole and there is a linear correlation between coronary flow and the diastolic intracoronary pressure measured with maximal myocardial hyperemia. FFR is calculated as the ratio of the pressure distal to the stenosis (Pd) to the pressure proximal to the stenosis (Pa) during maximal myocardial hyperemia. The mean pressures of Pd and Pa during a whole cardiac cycle are currently used for FFR calculation, instead of the pressure during diastole. More precisely, FFR should be calculated as (Pa−Pv)/(Pd−Pv), taking into consideration the influence of central venous pressure (Pv). However, Pv is extremely small compared with Pd or Pa, except in special cases, so it is generally assumed that Pv ≈0, and FFR is often calculated as Pd/Pa.[563,711]

Theoretically, the FFR values range from 0.0 to 1.0, with 1.0 representing a normal coronary artery. The FFR values indicate the extent to which blood flow in the target coronary artery is reduced by stenosis compared with the estimated flow in the absence of stenosis. For example, FFR=0.60 indicates that a stenosis has reduced coronary blood flow to 60% of normal.[712]

Measurement of the intracoronary pressure is performed by using a pressure guidewire. A typical pressure guidewire has almost the same shape as a guidewire for PCI, and a pressure sensor located near the proximal end of the radiopaque part (≈3 cm from the tip) is used to measure the intracoronary pressure. A monorail-type catheter has also been developed for measuring intracoronary pressure and can be used to measure FFR.

The procedure for measurement of FFR is as follows. First, the pressure guidewire is calibrated outside the body. It is then inserted into the guiding catheter and the pressure sensor is aligned with the tip of the guiding catheter, after which the pressure of the pressure sensor is equalized with that of the guiding catheter. Intracoronary administration of a nitrate is performed to prevent coronary spasm due to guidewire insertion, and the diameter of the coronary artery is kept constant between maximal hyperemia and baseline. Next, the pressure guidewire is advanced to the distal end of the coronary artery segment for measurement and a vasodilator (adenosine, ATP, papaverine hydrochloride, nicorandil, etc.) is administered to induce myocardial hyperemia, followed by simultaneous measurement of the distal pressure (Pd) using the pressure guidewire and the proximal pressure (Pa) at the tip of the guiding catheter during myocardial hyperemia to provide data for calculation of FFR. Subsequently, the pressure guidewire may be pulled back slowly while measuring the coronary pressure to determine the distribution of coronary artery lesions and to identify the lesion causing myocardial ischemia (pullback pressure measurement). Finally, the pressure sensor on the pressure guidewire is aligned with the tip of the guiding catheter again to confirm that there has been no pressure drift during measurement.

### 19.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

#### 19.2.1 Objectives of FFR Measurement

The objectives of measuring FFR are (1) to judge whether coronary artery stenosis is causing myocardial ischemia, (2) to evaluate the extent of reduction in coronary blood flow, (3) to judge the indications for coronary revascularization and select appropriate treatment, (4) to predict the prognosis, and (5) to assess the improvement of coronary flow after revascularization.

### 19.2.2 Indications

Measurement of FFR is indicated in patients with coronary artery stenosis who have not undergone assessment of ischemia using other methods for diagnosing myocardial ischemia, or in whom assessment of ischemia has been performed by other methods but the diagnosis of myocardial ischemia remains unclear. In general, lesions causing moderate stenosis (30–70% stenosis) on coronary angiography are the best indication.[568] However, FFR may be positive in a stenosis that appears to be mild on angiography or negative in an angiographically severe stenosis.[710,713] Therefore, if the diagnosis of myocardial ischemia is unclear in patients with mild or severe stenosis, FFR may be measured, if it can be done safely. In patients with serial lesions and diffuse lesions, coronary plaques present in the same vessel may collectively cause significant impairment of blood flow even if individual stenoses look mild on coronary angiography. Therefore, these lesions also represent a good indication for FFR measurement.[714,715]

Multivessel disease is another good indication for measurement of FFR. In patients with multivessel disease, it is often difficult to accurately assess the presence and extent of myocardial ischemia by coronary angiography or noninvasive diagnostic methods.[716] FFR allows accurate assessment of blood flow on the basis of each coronary artery, even in the presence of multivessel disease.[314] In studies where FFR was measured in patients who were judged to have multivessel disease on coronary angiography, the number of diseased vessels was changed and the treatment plan was modified in many patients. In addition, outcomes were better when treatment was modified according to the FFR findings than when treatment was selected without taking account of the FFR results.[717,718]

Left main coronary artery disease is another setting in which accurate assessment of myocardial ischemia is difficult using coronary angiography or noninvasive diagnostic methods, and this is accordingly a good indication for FFR measurement. It is reported that prognosis was good when coronary revascularization was performed based on positive results of FFR measurement and also when revascularization was deferred in the case of negative FFR.[719,720] For evaluation of left main coronary artery disease, the pressure guidewire should be inserted into the left anterior descending artery or left circumflex artery and is better to be placed into the coronary artery (left anterior descending or left circumflex) with little or no stenosis. It needs to be borne in mind that FFR values can be affected even when the pressure wire is positioned in a nondiseased vessel in the presence of hemodynamically severe stenosis in the vessel opposite to that in which the pressure wire is placed. In such a case, care should be exercised when interpreting the findings.[721–723]

It has been reported that stenotic lesions in bypass grafts can be assessed by FFR, but it should be noted that evidence is limited compared with that for native coronary lesions.[724]

FFR can be measured to assess the effect of coronary revascularization (i.e., the extent of improvement in myocardial blood flow after revascularization). In particular, the FFR values measured after balloon dilatation of lesions and after stent implantation have been reported to be associated with subsequent clinical outcomes.[725–727]

### 19.2.3 Contraindications

FFR cannot be measured when administration of vasodilators to induce myocardial hyperemia is contraindicated, such as in patients with drug allergies or asthma in the case of adenosine. Even when use of adenosine is contraindicated, availability of other agents may allow FFR measurement to be performed. In lesions with total occlusion, FFR measurement is impossible because the distal pressure cannot be measured by the pressure guidewire.

In patients with ST-elevation myocardial infarction, it is considered that achieving maximal hyperemia in the infarct-related vessel is impossible because of the microcirculatory dysfunction and accordingly the measurement of FFR is not recommended. However, the measurement of FFR in nonculprit lesions (those not responsible for myocardial infarction) has been reported to be unaffected by infarction,[728] and can be performed during the same PCI procedure for the culprit lesion in patients with ST-elevation myocardial infarction. Treatment of nonculprit lesions that cause significant ischemia according to the FFR values has been reported to be effective on a cost–benefit basis. The measurement of FFR is not recommended in extremely tortuous or extensively calcified lesions because insertion of the pressure guidewire is considered to be dangerous or impossible or the FFR values might not be reliable due to the accordion phenomenon.

### 19.2.4 Diagnostic Performance for Myocardial Ischemia

A study that assessed the accuracy of FFR for diagnosing myocardial ischemia (using FFR <0.75 as the criterion for significant ischemia) in comparison with exercise ECG, dobutamine stress echocardiography, and stress myocardial scintigraphy showed a sensitivity of 88%, specificity of 100%, positive predictive value of 100%, negative predictive value of 88%, and diagnostic accuracy of 93%.[568] In subsequent studies, the diagnostic accuracy of FFR was also found to be 75–97%.[729,730] Thus, FFR is currently considered to be the method with the highest accuracy for diagnosing myocardial ischemia caused by epicardial coronary artery stenosis.

### 19.2.5 FFR and Clinical Outcomes

It has been reported that better clinical outcomes can be obtained when coronary revascularization is performed on the basis of FFR measurement rather than angiographic findings.[314,731] Hence, if revascularization is scheduled for coronary lesions and myocardial ischemia has not been demonstrated by another method of functional assessment, FFR should be performed.

When FFR is ≤0.80, addition of revascularization to medical treatment has been reported to improve subsequent clinical outcomes compared with medical treatment alone, with the improvement of clinical outcomes being mainly due to a decrease in future emergency revascularization.[315,732] Accordingly, coronary revascularization should be considered when FFR is ≤0.80. Conversely, it has been reported that the prognosis is favorable when FFR is >0.80, even if revascularization is not performed,[314,732–734] suggesting that coronary revascularization is not required for lesions with FFR >0.80. However, correction of coronary risk factors should be actively implemented after revascularization is differed based on negative FFR.

### 19.2.6 Interpretation of FFR Values

#### a. Cutoff Value of FFR for Myocardial Ischemia

The cutoff value of FFR for myocardial ischemia is <0.75.[568] This value was determined by comparison with multiple

noninvasive diagnostic methods for ischemia. Follow-up studies have provided support for a cutoff value of 0.75–0.80, with an FFR of 0.75–0.80 being considered the gray zone for myocardial ischemia.[729,730] FFR is an index of the severity of blood flow impairment caused by epicardial coronary artery stenosis. Although FFR <0.75 is likely to be associated with myocardial ischemia, FFR ≥0.75 can also be associated with ischemia in the presence of microvascular disease.

#### b. Cutoff Value of FFR for Revascularization

The cutoff value of FFR when deciding the indication for coronary revascularization is ≤0.80, because clinical outcomes improved when FFR ≤0.80 was used as the cutoff value for revascularization in large-scale clinical studies.[314,315,732] A meta-analysis and a large prospective registry study have also supported a cutoff value of 0.75–0.80 for improvement of clinical outcomes by coronary revascularization.[735,736] On the other hand, for FFR ≥0.75, the prognosis was reported to be favorable even if revascularization of lesions was deferred.[733,734] Therefore, FFR of 0.75–0.80 is considered to be the gray zone for revascularization.

#### c. Interpretation of FFR as a Continuous Variable

Although FFR ≤0.80 is used as the cutoff value when deciding the indication for revascularization, FFR is actually a continuous variable that ranges from 0 to 1.0. When FFR is ≤0.80, impairment of blood flow due to epicardial coronary artery stenosis is more severe as FFR values become lower. Conversely, when the FFR is >0.80, higher FFR values mean less impairment of blood flow. Therefore, the effectiveness of coronary revascularization and medical therapy, as well as subsequent clinical outcomes, will vary depending on the FFR value. In particular, there is a negative correlation between the FFR value and the incidence of cardiovascular events when revascularization is deferred.[735–737]

### 19.2.7 Determining the Indication for Coronary Revascularization

#### a. Indication for Revascularization

Coronary revascularization is indicated for lesions when the FFR is ≤0.80, based on reports that the addition of revascularization to medical therapy leads to better clinical outcomes than drug therapy alone when the FFR of a lesion is ≤0.80.[315,732] However, this should not be interpreted as meaning that revascularization is required for all lesions with FFR ≤0.80. If the FFR is ≤0.80, but the lesion is diffuse or there is small vessel disease where revascularization is not likely to be effective or the lesion is so complex that revascularization cannot be performed safely, medical therapy instead of revascularization might be an appropriate clinical decision. Performing revascularization can generally be justified if FFR is ≤0.80 at the time of the procedure.

#### b. Avoiding Revascularization

Revascularization should generally be avoided when the FFR is >0.80, because it has been reported that clinical outcomes can be worse after revascularization of such lesions compared with medical therapy.[314,732–735]

#### c. Approach to Lesions With a "Gray Zone" FFR

Studies have found different results when the FFR is in the range of 0.75–0.80, and there is no consensus on the treatment strategy.[738,739] Therefore, treatment should be decided by comprehensive consideration of patient and lesion characteristics in addition to the FFR value.

#### d. Selection of the Revascularization Method (PCI or CABG)

There is considerable evidence regarding the use of FFR together with PCI, but only limited evidence is available for CABG. In previous reports, FFR ≤0.80 was used as the cutoff value when deciding the indication for CABG. This is the same cutoff value as for PCI, suggesting that it may be reasonably used for CABG.[740,741] It should be noted, however, that there has not been adequate verification of whether this is the optimal cutoff value for CABG.

### 19.2.8 Evaluation After Coronary Revascularization

Measurement of the FFR after revascularization allows the effectiveness of treatment to be assessed. For example, improvement of the FFR of a lesion from 0.60 to 0.90 after treatment means that revascularization has improved coronary blood flow by 30 percentage points and has probably alleviated myocardial ischemia.[712] In addition, the FFR values measured after catheter procedures have been reported to be associated with subsequent clinical outcomes and can thus be used as the endpoint for catheter treatment.

A good clinical outcome had been reported at 2 years after balloon angioplasty when the postprocedural FFR value is ≥0.90,[725] and a low incidence of events has been reported at 6 months after bare metal stent implantation when the FFR is ≥0.90.[727] In addition, the clinical outcome is better after DES implantation when the FFR is ≥0.89–0.92 than with lower FFR values.[727,742,743] Although there were some differences in the endpoint values among the studies, higher FFR values were associated with lower clinical event rates. However, it is often difficult to achieve high postprocedural FFR values in patients with diffuse or long lesions. Attempts to achieve a high FFR value may lead to an increase in the total stent length and number of stents, as well as increasing the risk of complications and medical costs. Thus, it should be noted that although higher FFR values after PCI are associated with better clinical outcomes, the association between making extensive efforts to improve the FFR value and better clinical outcomes remains to be verified.[744]

### 19.2.9 Economic Benefits of FFR-Based Coronary Revascularization

It has been reported that FFR-guided PCI not only improves clinical outcomes compared with angiography-guided PCI, but also achieves better medical economy,[572] primarily because medical costs are reduced by avoiding unnecessary coronary revascularization.

It has also been reported that for lesions with significantly reduced FFR, the initial cost of revascularization is higher than that of medical therapy alone, but the cost eventually becomes similar. This is because avoiding coronary revascularization for lesions with significantly reduced FFR results in a later increase in the revascularization rate, leading to escalation of medical costs. Given that clinical outcomes are better compared with medical therapy alone and long-term medical costs are equivalent, performing revascularization of lesions with significantly reduced FFR seems to represent an effective use of medical resources.[745]

**Table 43. Recommendations and Levels of Evidence for Invasive Intracoronary Pressure Measurements for the Diagnosis of Chronic Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| FFR/iFR are recommended for assessing hemodynamic significance of epicardial coronary artery stenosis | I | A | A | I |
| FFR/iFR are recommended for decision-making on PCI indication | I | A | A | I |
| FFR/iFR are considered for decision-making on CABG indication | IIb | B | B | IVa |
| FFR might be useful for assessing post-PCI results | IIb | C | B | IVa |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

### 19.2.10 Instantaneous Wave-Free Ratio (iFR)

Similar to FFR, iFR is another parameter of functional coronary stenosis that is based on coronary artery pressure obtained by a pressure guidewire.[746] iFR is also calculated as the ratio of the pressure distal to the stenosis (Pd) to the pressure proximal to the stenosis (Pa). However, FFR is measured during drug-induced maximal myocardial hyperemia, whereas iFR is measured under resting conditions. Also, the FFR is the mean Pd/Pa ratio over the entire cardiac cycle, whereas iFR is measured during the last 75% of diastole, which is called the wave-free period. Accordingly, iFR is calculated as $Pd_{\text{wave-free period}}/Pa_{\text{wave-free period}}$, and coronary artery stenosis is judged to be hemodynamically significant when iFR is ≤0.89.[747] The same cutoff value (iFR ≤0.89) is used for diagnosis of myocardial ischemia and as the indication for coronary revascularization.[748,749]

The diagnostic accuracy of iFR vs. FFR has been tested by head-to-head comparison, as well as by comparison involving other physiological diagnostic methods for ischemia, and these studies have shown that iFR is approximately equivalent to FFR.[750–755] In addition, 2 large-scale clinical studies demonstrated that iFR-guided coronary revascularization was not inferior to FFR-guided coronary revascularization, indicating that iFR can be used as an alternative to FFR.[748,749] As well as iFR, some other indices based on resting coronary pressures have also been reported, but further assessment is required to determine their clinical usefulness.[756–758] Recommendations and levels of evidence for this procedure are shown in **Table 43**.

## 20. Measurement of Coronary Flow Velocity

### 20.1 Characteristics and Technical Aspects

Measurement of coronary blood flow velocity is generally performed in order to obtain the CFVR. The CFR (CFVR) is an index of the increase in coronary flow (velocity) during myocardial stress compared with at rest, and is defined as the ratio of coronary blood flow (velocity) during stress to coronary blood flow (velocity) at rest.[759] PET can be used to quantitatively assess myocardial blood flow and calculate the CFR,[760,761] but CFVR is more often calculated from coronary blood flow velocity data obtained with echocardiography or a Doppler guidewire.[318,762] To calculate the CFVR based on the coronary blood flow velocity, it is assumed that the vessel diameter is the same at rest and under stress, which means the ratio of coronary blood flow velocity during stress to that at rest is the same as the coronary blood flow ratio. Therefore, the CFVR (the ratio of coronary blood flow velocity) is calculated to obtain CFR.

In the past, catheter-based Doppler blood flow measurement was done in some cases,[763] but the CFVR is now measured during cardiac catheterization by either a guidewire with a Doppler sensor or a dual guidewire equipped with both a Doppler sensor and a pressure transducer.[764,765] When the CFVR is measured with a guidewire, intracoronary nitrate is administered before the wire is inserted into the coronary artery to prevent coronary spasm and achieve maximal vasodilation. To assess the influence of coronary stenosis on the CFVR, the wire should be positioned such that the Doppler sensor is located at a distance of 5–10 vessel diameters (≥20 mm) from the stenosis. It should also be noted that the sample volume is located 5 mm distal to the sensor of the wire. In 10–15% of patients, it is difficult to obtain a clear blood flow signal. In such cases, the wire should be manipulated to adjust the position and direction of the Doppler sensor in order to obtain a blood flow signal of the highest quality possible.[730]

CFVR can be calculated as the ratio of the average peak velocity (APV) with myocardial hyperemia to that at rest (APV hyperemia/APV rest). Maximal myocardial hyperemia is induced by continuous intravenous infusion or intracoronary administration of adenosine or ATP, intracoronary administration of papaverine hydrochloride, or intracoronary administration of nicorandil, etc. The CFVR can also be determined during cardiac catheterization by the thermodilution method using a temperature sensor attached to a pressure guidewire. With this method, a pressure guidewire is inserted into the target coronary artery and bolus intracoronary administration of saline at room temperature is performed through the guiding catheter, followed by measurement of the mean transit time (Tmn). Coronary flow velocity can be estimated by the inverse Tmn, and then the CFVR is calculated as the ratio of inverse Tmn during maximal myocardial hyperemia to Tmn at rest.[766,767]

Transthoracic or transesophageal echocardiography can be performed for noninvasive visualization of coronary flow velocity signals by color Doppler imaging. The sample volume is set above the coronary flow velocity signals using a pulsed Doppler method so that temporal changes in coronary flow velocity signals can be recorded, allowing the CFVR to be calculated from the mean flow velocity measured at rest and that measured during maximal hyperemia.[762]

## 20.2 Significance in the Diagnosis of Chronic Coronary Heart Disease

### 20.2.1 Objectives of Measuring CFR and CFRVR

CFR and CFVR are indices that reflect myocardial ischemia caused by epicardial coronary artery lesions and coronary microvascular dysfunction. As such, these indices are used to determine the severity of hemodynamic stenosis caused by coronary lesions and to assess coronary microvascular dysfunction. Because it is impossible to separate the contribution of epicardial coronary artery lesions and microvascular dysfunction to myocardial ischemia by CFR, care should be exercised when interpreting the results when deciding the indications and effectiveness of PCI.

### 20.2.2 Indications

Coronary flow velocity can be measured to assess the hemodynamic severity of coronary stenosis,[318] and can also be used to assess the severity of coronary microvascular dysfunction.[768]

### 20.2.3 Contraindications

Measurement of CFR or CFVR is impossible when administration of vasodilators to induce maximal myocardial hyperemia is contraindicated, such as in patients with drug allergies or asthma in the case of adenosine. Even when adenosine is contraindicated, other agents may be available that allow measurement of CFR or CFVR. Insertion of a guidewire should be avoided for lesions where this is considered to be dangerous or impossible, such as tortuous or heavily calcified lesions. In patients with total occlusion, the retrograde or anterograde collateral flow velocity can be detected distal to the occlusion if insertion of a Doppler guidewire with a microcatheter is successful after crossing the lesion with the guidewire, allowing CFR or CFVR to be calculated.

### 20.2.4 Diagnostic Performance

The diagnostic performance of CFR or CFVR for myocardial ischemia using a cutoff value <2.0 has been reported to be as follows: sensitivity of 86–92%, specificity of 89–100%, diagnostic accuracy of 89–96%, positive predictive value of 84–100%, and negative predictive value of 77–95%.[729,730]

### 20.2.5 Interpretation of Measured Values

In general, myocardial ischemia is judged to be present when CFR or CFVR is <2.0,[729,730] but the normal value varies among reports. In animals and healthy adults, the CFR or CFVR is reported to be in the range of 3.5–5.[759,769,770] In patients with coronary risk factors but without coronary stenosis, the CFR has been reported to be ≈2.6–2.7.[771,772]

Hemodynamically significant epicardial coronary artery lesions and coronary microvascular dysfunction can be ruled out if the CFR or CFVR is ≥2.0 and myocardial ischemia is negative. If the CFR or CFVR is <2.0 and myocardial ischemia is positive, myocardial ischemia is considered to be due to epicardial coronary artery lesions or microvascular obstruction, or both causes. Even if myocardial ischemia is positive with the CFR or CFVR, epicardial coronary artery lesions cannot be identified as the cause; hence, these are not suitable indices for deciding the indications for revascularization.

It should also be noted that CFR (and CFVR) are calculated from the ratio of blood flow (velocity) at maximal myocardial hyperemia to blood flow (velocity), at rest and thus are affected by factors that can alter both resting and hyperemic blood flow (velocity). Thus, these parameters are influenced by hemodynamic changes (heart rate and blood pressure), preload and afterload of the left ventricle, left ventricular systolic function, cardiac mass, etc.[729,730]

### 20.2.6 Relationship to Clinical Outcomes

Several studies have found an association between CFR or CFVR and prognosis. The number of cardiovascular events is increased when CFR or CFVR is <2.0 compared with when these parameters are ≥2.0.[318,762,773,774] Regarding the indications for coronary revascularization, it has been shown that deferral of revascularization in intermediate stenoses is safe when the CFR or CFVR is ≥2.0.[279] In terms of postrevascularization assessment, it has been shown that patients with both ≤35% residual stenosis and a CFR or CFVR ≥2.5 following balloon angioplasty have subsequent favorable outcomes.[775]

### 20.2.7 Combined Coronary Flow Velocity and Intracoronary Pressure Measurement

CFR or CFVR does not allow separate assessment of the effect of epicardial coronary artery lesions and coronary microvascular dysfunction. However, it has been proposed that adding intracoronary pressure information to coronary flow velocity data may help to separate the influence of coronary artery lesions from that of coronary microvascular dysfunction. Simultaneous measurement of coronary flow velocity and intracoronary pressure is possible by using a dual sensor guidewire.

#### a. Baseline Stenosis Resistance (BSR) Index

The BSR index is a measure of the vascular resistance caused by coronary stenosis at rest, and it is specific for epicardial coronary artery stenosis. It is calculated as: baseline Pa – baseline Pd/baseline APV.[750]

#### b. Hyperemic Stenosis Resistance (HSR) Index

The HSR index measures the vascular resistance caused by coronary stenosis at maximal myocardial hyperemia, and it is also specific for epicardial coronary artery stenosis. It is calculated as: hyperemic Pa – hyperemic Pd/hyperemic APV.[776]

#### c. Microvascular Resistance (MVR)

MVR specifically assesses the vascular resistance of the coronary microcirculation. MVR at rest is calculated as: baseline Pd/baseline APV, and MVR at maximal myocardial hyperemia is calculated as: hyperemic Pd/hyperemic APV.[777]

#### d. Index of Microcirculatory Resistance (IMR)

The IMR specifically assesses the vascular resistance of the coronary microcirculation, which is determined by using a pressure guidewire with the thermodilution method. IMR is calculated as the product of mean hyperemic Pd and hyperemic Tmn.[778]

#### e. Lack of Agreement Between FFR and CFR or CFVR

By measuring both FFR and CF(V)R in the same coronary artery, more detailed assessment of coronary pathophysiology is possible. If both FFR and CF(V)R are negative for ischemia in the same coronary artery, it can be

**Table 44. Recommendations and Levels of Evidence for Invasive Intracoronary Coronary Flow Velocity Measurements**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| CF(V)R can be used to assess the degree of myocardial ischemia as the combination of epicardial coronary artery stenosis and microvascular disease | IIa | B | B | IVa |
| BSR/HSR might be considered for the assessment of epicardial coronary artery stenosis | IIb | C | B | IVb |
| IMR/MVR might be considered for the assessment of microvascular disease | IIb | C | B | IVa |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

concluded that coronary blood flow is adequate and neither coronary artery lesions nor dysfunction of the coronary microcirculation is causing myocardial ischemia. On the other hand, if FFR and CF(V)R are both positive for ischemia, there is likely to be significant hemodynamic stenosis in the target coronary artery. However, discordant results for FFR and CF(V)R have been reported in about 30–40% of lesions. When CF(V)R is positive for ischemia and FFR is negative, this may indicate the presence of coronary microvascular dysfunction. On the other hand, if CF(V)R is negative for ischemia and FFR is positive, the coronary microcirculation should be adequate and it can also be suggested that coronary artery lesions are not causing significant stenosis. In this setting, the decrease in FFR may result from an increase in the pressure gradient due to a marked increase in coronary blood flow (velocity) at maximal myocardial hyperemia, although coronary stenosis is not so severe. This may also represent a state in which coronary blood flow (velocity) is maintained while coronary artery pressure decreases.[213,777,779] Recommendations and levels of evidence for this procedure are shown in **Table 44**.

# II. Risk Assessment and Management

## 1. Comprehensive Risk Management

Patients with coronary heart disease have a higher risk of recurrent cardiovascular events than persons receiving primary prevention, and various interventions are important for these patients, including lifestyle modification, exercise, diet, and drug therapy. Risk factors for coronary heart disease include hypertension, diabetes mellitus, dyslipidemia, CKD, and smoking. Recent large-scale clinical studies have demonstrated the usefulness of aggressive antihypertensive therapy for patients with hypertension. However, there is little Japanese evidence regarding the value of strict antihypertensive therapy in hypertensive patients with coronary heart disease, and the current goal of treatment is a blood pressure <140/90 mmHg.

In patients with multiple risk factors, such as prior myocardial infarction, diabetes mellitus, CKD, dyslipidemia, smoking, and a positive family history, the target blood pressure is set at <130/80 mmHg after confirming the absence of significant coronary artery stenosis and myocardial ischemia or changes on ECG. In patients with concomitant diabetes mellitus, the age, duration of diabetes mellitus, complications, and risk of hypoglycemia must be considered. According to the 2016 Japan Diabetes Society Clinical Practice Guideline, the target HbA1c is ≤7.0% for prevention of complications.[780]

Management of dyslipidemia with aggressive lipid-lowering therapy, primarily statins, has been well documented in patients requiring secondary prevention. The 2017 Guidelines for Prevention of Atherosclerotic Cardiovascular Disease[4] set a target of <100 mg/dL for LDL-cholesterol in patients who require secondary prevention. For patients who have FH, ACS, or high-risk diabetes mellitus and a high risk of recurrent events despite secondary prevention, stricter lipid-lowering therapy is recommended, with LDL-cholesterol <70 mg/dL being the target, as in Western guidelines. Patients receiving secondary prevention often have these comorbidities, so comprehensive management is essential.

Prevention of cardiovascular events in patients with coronary heart disease is important both clinically and in terms of medical economics, because these events are more frequent in such patients than in the general population. Comprehensive risk management is clearly important because epidemiological studies have shown that hypertension, diabetes mellitus, dyslipidemia, smoking, and CKD are risk factors for arteriosclerosis and development of cardiovascular events, and many patients have multiple risk factors, increasing the risk of events occurring. Observational studies performed in Western countries have shown that better management of multiple risk factors improves the long-term prognosis of patients with coronary heart disease.[781,782] In Japan, the J-DOIT3 study (published in 2017) demonstrated the usefulness of aggressive long-term intervention for control of glucose, blood pressure, lipids, and obesity, although the study population consisted of patients with diabetes mellitus receiving primary prevention.[783] Aggressive intervention, including lifestyle modification/exercise,[784] dietary therapy, and drug therapy, is important for preventing recurrent cardiovascular events.

### 1.1 Hypertension

Hypertension is a major risk factor for coronary heart disease and cerebrovascular disease, and is also the most common coronary risk factor encountered in daily clinical practice. According to NIPPON DATA 2010, 43 million

persons were estimated to have hypertension in Japan in 2010.[785] An association between hypertension and development of cardiovascular disease has been clarified by both domestic and foreign cohort studies. EPOCH-JAPAN, a meta-analysis of major cohort studies performed in Japan, showed that the risk of death from cardiovascular disease increases as the blood pressure rises above the optimal level (systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg).[786]

On the other hand, large-scale clinical studies performed in Western countries in the 1990 s consistently set a higher target for the blood pressure and found no further decrease in events if it was reduced below 140/90 mmHg. Accordingly, the target is set at 140/90 mmHg in the guidelines of Japan, the USA, and Europe. A recent meta-analysis also showed that all-cause death, cardiovascular death, myocardial infarction, and heart failure were all reduced by lowering the blood pressure, but an additional improvement was not noted with reduction of systolic blood pressure to <140 mmHg. As an exception, the incidence of stroke was decreased by further reduction of the blood pressure. Thus, the effect of blood pressure reduction on these events generally seems to level off around 140/90 mmHg. On the other hand, excessive reduction of the blood pressure (especially the diastolic pressure) has been reported to decrease coronary perfusion pressure, inducing myocardial ischemia and an increase in cardiovascular events (J-shaped curve for the benefits of blood pressure reduction). In the 2014 Guideline for Treatment of Hypertension (JSH2014),[787] published by the Japanese Society of Hypertension in 2014, the target blood pressure was set at <140/90 mmHg in patients with coronary heart disease. This guideline also stated that the target blood pressure should be <130/80 mmHg in patients with multiple risk factors, such as a history of myocardial infarction, diabetes mellitus, CKD, dyslipidemia, smoking, and positive family history, after confirming the absence of significant coronary artery stenosis and myocardial ischemia or ECG changes.

Interestingly, the SPRINT study demonstrated the usefulness of strict blood pressure control, in contrast to the fact that there has been no change in the target blood pressure recommendations over the past 20 years.[788] The study showed that aggressive antihypertensive therapy targeting a systolic blood pressure <120 mmHg was associated with a significant reduction in the composite endpoint of ACS, stroke, decompensated heart failure, and cardiovascular death, as well as a reduction in all-cause death, compared with standard therapy (target blood pressure <140 mmHg) in patients at high risk of cardiovascular disease. However, it should be noted that the SPRINT trial excluded patients with a history of diabetes mellitus, CKD, heart failure, or stroke, which represent important subpopulations of the patients receiving secondary prevention in real-world clinical settings. A meta-analysis of 42 studies (144,220 patients) also showed a significant reduction in the incidence of cardiovascular events when the systolic blood pressure was maintained at 120–124 mmHg, which is lower than the conventional target blood pressure.[789] Based on such new evidence, the current ACC/AHA guidelines for management of hypertension set the target at <130/80 mmHg in hypertensive patients with chronic coronary heart disease.[790] On the other hand, there is little evidence about the efficacy of aggressive antihypertensive therapy for hypertensive Japanese patients with coronary heart disease. At present, 140/90 mmHg should still be the target for secondary prevention, as recommended by the Japanese Society of Hypertension, and 130/80 mmHg should be the target for patients with the abovementioned conditions.

## 1.2 Diabetes Mellitus

Previous epidemiological studies have shown that diabetes mellitus (DM) increases the risk of stroke and cardiovascular disease by about 2- to 4-fold.[791,792] A meta-analysis also demonstrated that a 1% increase in HbA1c was associated with an 18% increase in cardiovascular events.[793] In addition, it has been reported that patients with cardiovascular disease secondary to DM have higher rates of cardiovascular mortality and recurrent events.[794,795]

Based on the results of observational studies, which showed that an increase in events is associated with elevation of blood glucose, it was speculated that development of macroangiopathy could be suppressed by reducing the blood glucose level. Subsequently, intervention studies using strict glycemic control were conducted, including ACCORD,[796] ADVANCE,[797] and VADT,[798] but these studies revealed that several years of intensive management did not reduce the incidence of macroangiopathy. In fact, the ACCORD study found a significant increase in mortality in the intensive treatment group. The study indicates that this outcome occurred because strict glycemic control increases the frequency of hypoglycemia. In contrast, early glycemic control has been reported to reduce long-term complications and mortality (legacy effect), and early glycemic control, while avoiding hypoglycemia is considered to be important.[799]

The glycemic control target must consider the patient's age, duration of DM, comorbidities, and risk of hypoglycemia among other factors. In the 2016 Japan Diabetes Society Clinical Practice Guideline published by the Japan Diabetes Society, the target HbA1c is set at ≤7.0% from the viewpoint of preventing complications. Metformin is recommended as a globally accepted first-line antidiabetic drug. Use of SGLT2 inhibitors[800,801] and GLP-1 receptor agonists,[802] which were found to reduce cardiovascular events in large-scale clinical studies reported in 2017, has also been recommended, but it remains unclear which patients should be treated with these drugs. Whichever medication is used, more attention must be paid to hypoglycemia, adverse reactions, and potential effects on the cardiovascular system.

Comprehensive management, including control of blood pressure and lipid-lowering therapy with statins, is essential because patients with DM have a high incidence of cardiovascular events. The 2017 Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases state that patients who have DM associated with noncardiogenic cerebral infarction, PAD, CKD, metabolic syndrome, or smoking are a high-risk population for secondary prevention, in addition to patients with FH and ACS, and recommend aggressive lipid-lowering therapy with LDL-cholesterol <70 mg/dL as the target.

## 1.3 Dyslipidemia

Dyslipidemia is a generic term that refers to elevation of total cholesterol, LDL-cholesterol (LDL-C), and/or triglycerides, or a low level of HDL-cholesterol. The greatest amount of evidence, including intervention studies, has been

**Table 45. Lipid Management Targets for Patients With Different Risk Category**

| Therapeutic principle | Management category | Lipid management target (mg/dL) | | | |
|---|---|---|---|---|---|
| | | LDL-C | Non-HDL-C | TG | HDL-C |
| **Primary prevention** Drug therapy should be considered after lifestyle modification | Low risk | <160 | <190 | <150 | ≥40 |
| | Moderate risk | <140 | <170 | | |
| | High risk | <120 | <150 | | |
| **Secondary prevention** Drug therapy should be considered together with lifestyle modification | History of CAD | <100 (<70)* | <130 (<100)* | | |

* For patients who are also suffering from high-risk conditions, such as FH, ACS, and diabetes complicated by other high-risk conditions shown in **SubTable b**, stricter LDL-C control should be considered, with a level of <70 mg/dL as the target.

- Although non-drug therapy is used as a standard means for achieving the management target in primary prevention, drug therapy should be considered for patients with low risk if the LDL-C level is ≥180 mg/dL. The possibility of FH should also be considered (see Chapter 5 of the source document).
- Achieving the LDL-C management target should be the first goal, and reaching the non-HDL-C management target should be the next goal after the first goal has been achieved. Managing the TG and HDL-C levels is important during this process.
- These values are challenging goals by utmost effort; a 20–30% reduction in LDL-C levels for primary prevention (low or moderate risk) and a decrease of ≥50% for secondary prevention are also possible targets.
- For elderly patients (aged ≥75 years), refer to Chapter 7 of the source document.

**SubTable. Patient Conditions That Require Stricter Management in Secondary Prevention**

| | |
|---|---|
| **a** | Familial hypercholesterolemia (FH)<br>Acute coronary syndrome (ACS)<br>Diabetes mellitus (DM) |
| **b** | Noncardiogenic cerebral infarction<br>Peripheral artery disease (PAD)<br>Chronic kidney disease (CKD)<br>Metabolic syndrome<br>Overlap of major risk factors<br>Smoking |

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides. (Reproduced from Kinoshita et al 2018,[4] with permission.)

accumulated for LDL-C, although associations between all of these lipids (including nonHDL-cholesterol) and cardiovascular disease have been reported.[803–809] Many Western epidemiological studies, including the Framingham heart study, have shown that a high LDL-C level is associated with an increased incidence of coronary heart disease and mortality.[810] The CIRCS study investigated the incidence of coronary heart disease in Japanese patients, using LDL-C <80 mg/dL as the control value, and found that the incidence was increased 1.35-fold in the 80–99 mg/dL group, 1.66-fold in the 100–119 mg/dL group, 2.15-fold in the 120–139 mg/dL group, and 2.8-fold in the ≥140 mg/dL group.[811]

Large-scale clinical studies performed in Western countries since the 1990s have demonstrated that lipid-lowering therapy with statins reduces cardiovascular events. A 2005 meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaborators showed that reducing LDL-C by 1 mmol with statin therapy was associated with 21% reduction of cardiovascular events.[812] On the other hand, there have been few Japanese interventional studies assessing cardiovascular events in patients receiving secondary prevention. Instead, most interventional studies have assessed changes in coronary plaque by IVUS. Studies such as ESTABLISH,[813] JAPAN-ACS,[814] and PRECISE-IVUS[815] have shown that aggressive lipid-lowering therapy with statins or the combination of statins and ezetimibe leads to plaque regression. Recent studies have also demonstrated that adding other cholesterol-lowering drugs, such as ezetimibe and PCSK9 inhibitors, to statin therapy can further reduce cardiovascular events.[816,817] Based on the results of these clinical studies, the following statement was added to the 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation: consider combining PCSK9 inhibitors or ezetimibe if LDL-cholesterol does not reach the target level of <70 mg/dL even with use of the maximum tolerable dose of a statin.[818] In Japan, the LDL-C target for patients with a history of coronary heart disease receiving secondary prevention is <100 mg/dL. In the 2017 revision of the Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases, it also states that patients receiving secondary prevention should be managed with a target LDL-C level <100 mg/dL, and if this is difficult to achieve, reduction of LDL-C by at least 50% should be attempted (**Table 45**).[4] However, more stringent lipid-lowering therapy is recommended for high-risk patients, such as those with FH, ACS, and high-risk diabetes mellitus, with an LDL-C level <70 mg/dL as the target, corresponding to the guidelines from Western countries (**Figure 18**).

The high doses of statins recommended in Western guidelines are not covered by health insurance in Japan, which only funds moderate statin doses, partly because there have been few Japanese interventional studies of

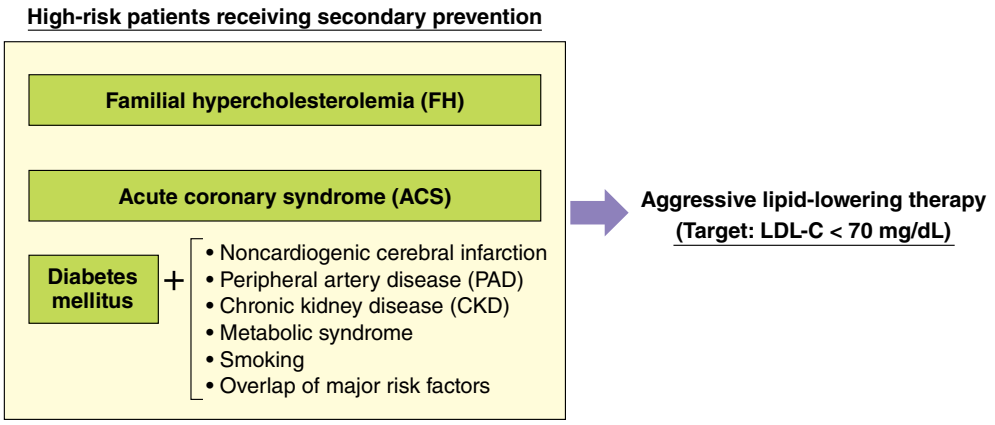



**Figure 18.** Patient conditions that require stricter management for secondary prevention. LDL-C, low-density lipoprotein cholesterol. (Reproduced from Kinoshita et al 2018,[4] with permission.)

lipid-lowering therapy for secondary prevention with cardiovascular events such as cardiovascular death as the endpoint, as mentioned above. Under these circumstances, the results of the REAL-CAD study were published in 2017. This study enrolled 14,774 patients aged 20–80 years with stable angina from 733 institutions nationwide, with the patients being randomly allocated to receive 1 mg or 4 mg of pitavastatin daily. Significant reduction of cardiovascular events (19%) was found in the 4-mg group. Notably, there was significant reduction of events such as all-cause death, myocardial infarction, and repeat revascularization, with similar results being obtained after stratification for age, sex, or other variables. In view of these findings, it is recommended that patients with stable angina should receive statin therapy at the highest possible dose within the scope of health insurance coverage.[819]

An increase in triglycerides, both fasting and nonfasting, is known to predict future coronary heart disease and stroke, as well as death, and monitoring triglycerides is an important part of risk management during statin therapy. The EMPATHY study performed in Japan demonstrated that elevation of triglyceride levels was associated with new-onset coronary heart disease in high-risk patients with diabetes mellitus receiving statins who had retinopathy and hypercholesterolemia.[820]

## 1.4 CKD

CKD is an important risk factor for arteriosclerosis. A large-scale registry study previously showed that the risk of all-cause death and cardiovascular disease increased as the eGFR declined in patients with an eGFR <60 mL/min/1.73 $m^2$.[821] The mortality rate of dialysis patients was 40-fold higher than that of controls without kidney disease, and it should be noted that over 50% of deaths were from cardiovascular disease.[822]

CKD patients often have hypertension and diabetes mellitus as the underlying diseases, making it important to screen for arteriosclerotic diseases in this patient population. Comprehensive risk management is also necessary. Although large-scale clinical studies have not demonstrated that statins are effective for secondary prevention in dialysis patients,[823,824] the efficacy of statins has been verified in CKD patients who were not on dialysis.[825,826] Therefore, statin therapy is recommended from the early stage of CKD. For management of blood pressure, antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker is recommended, especially in patients with proteinuria, because an organ protective effect can be expected with such treatment.[827,828]

## 1.5 Smoking

Cigarette smoking is an independent risk factor for cardiovascular disease, and it is clear that smoking promotes arteriosclerosis.[829,830] The incidence of coronary heart disease caused by smoking is known to increase in proportion to the extent and duration of smoking. Even at low levels, cigarette smoking is associated with a higher cardiovascular risk,[831] so cessation of smoking is strongly recommended for patients receiving secondary prevention or at high risk of cardiovascular disease. It is also a social responsibility to avoid passive exposure to cigarette smoke in homes, public facilities, and workplaces, because passive smoking is also associated with an increase in cardiovascular events.[832]

Observational studies have demonstrated that cessation of smoking significantly reduces the risk of cardiovascular events. In a Japanese observational study of patients with acute myocardial infarction, nonsmokers had a 61% lower risk of all-cause death than smokers.[833] According to a meta-analysis of patients with coronary heart disease, cessation of smoking reduced the relative risk of death by 36%.[834] Although these studies indicating an impact of smoking cessation were all observational, it should be recognized that cessation of smoking is no less effective than drug therapy for other risk factors. However, it is not uncommon to find that patients cannot quit smoking and continue to smoke because of nicotine dependence, even if guidance on quitting is provided. In such cases, use of drug therapy to assist smoking cessation should be considered, in addition to counseling. Currently, 12 weeks of treatment for smoking cessation is covered by health insurance in Japan, provided that the medical institution and patient

**Table 46. Recommendations and Levels of Evidence in Comprehensive Risk Management**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| In patients with coronary heart disease, comprehensive risk management should be undertaken, including blood pressure, glucose, lipids, and cessation of smoking | I | A | A | I |
| Blood pressure target is <140/90 mmHg in patients with coronary heart disease | I | A | A | I |
| In patients with overlapping risk factors, such as prior myocardial infarction, diabetes, CKD, dyslipidemia, smoking, or a positive family history, the goal is to achieve blood pressure <130/80 mmHg after confirmation of the absence of myocardial ischemia and ECG changes | IIa | B | B | II |
| Treatment target for diabetes is HbA1c <7.0% | IIa | B | B | II |
| During treatment of diabetes, attention should be paid to hypoglycemia | I | A | A | I |
| In patients with coronary heart disease, aggressive lipid-lowering therapy, primarily with statins, should be performed, with the target LDL-C level set at <100 mg/dL | I | A | A | I |
| In patients receiving secondary prevention who have FH, ACS, or high-risk diabetes, the target LDL-C level should be <70 mg/dL | IIa | B | B | II |
| Patients with coronary heart disease should be strongly advised to quit smoking | I | A | A | I |

COR, class of recommendation; GOR, grade of recommendation; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence.

meet certain conditions. Thus, treatment should be provided for a certain period together with ongoing guidance about cessation of smoking. Recommendations and levels of evidence for comprehensive risk management are shown in **Table 46**.

## 2. Additional Risk Factors and Biomarkers

### 2.1 Additional Risk Factors and Their Management

#### 2.1.1 Family History

Although the importance of a patient's family history has been recognized, few large-scale studies have examined the influence on coronary heart disease. Previous cross-sectional studies have shown that a family history of myocardial infarction is associated with an odds ratio of ≈2 for development of myocardial infarction, and that the risk increases synergistically with the presence of other risk factors such as hypertension and dyslipidemia.[835,836] Family history was also reported to be an independent risk factor for acute myocardial infarction in Japanese patients with acute myocardial infarction (odds ratio: 1.84, 95% CI: 1.30–2.62, P<0.01).[837] Furthermore, longitudinal studies have identified the family history as a significant risk factor for development of myocardial infarction, with a stronger influence in younger populations.[838,839] Even if other risk factors are negligible, a positive family history of cardiovascular disease has been shown to influence the occurrence of cardiovascular disease.[840] Thus, a positive family history is one of the most important risk factors, regardless of the presence or absence of other risk factors, and obtaining information about the family history is essential, especially in younger patients.

#### 2.1.2 Uric Acid

For many years, it has been debated whether hyperuricemia is a risk factor for atherosclerotic disease or not, and consensus has not been achieved.[841] Recent meta-analyses have suggested that the uric acid level may be an independent risk factor for hypertension and coronary heart disease.[842–844] However, although it is reasonable to use appropriate urate-lowering therapy to reduce the incidence of gout and kidney dysfunction associated with hyperuricemia, there is limited evidence from interventional studies about whether such therapy can reduce cardiovascular events, so further investigation is warranted.

#### 2.1.3 Obstructive Sleep Apnea

Although the prevalence of obstructive sleep apnea (OSA) is high among patients with cardiovascular disease, it is often underdiagnosed.[845] Therefore, it is important to consider the possibility of OSA and make an appropriate diagnosis. In patients with coronary heart disease, OSA is strongly associated with major cardiovascular events and increased mortality.[846,847] In patients with OSA and a history of coronary heart disease or multiple risk factors, CPAP therapy has been reported to reduce the mean 24-hour blood pressure, including the nighttime blood pressure.[848] Secondary prevention of major cardiovascular events with CPAP therapy has not been well documented; however, it is effective for improving sleep and quality of life. It has also been suggested that good adherence to CPAP therapy may have a secondary prevention effect.[849,850]

#### 2.1.4 Exercise

Many studies have demonstrated that cardiac rehabilitation, especially exercise therapy, is effective for secondary prevention of coronary heart disease.[851] Moderate aerobic exercise (walking, etc.) for a total of ≥30 min per day on at least 5 days per week is generally recommended. However, the type and intensity of exercise should be determined according to the patient's level of risk and general condition. The amount of physical activity performed during daily life should also be increased through use of stairs and outdoor activities.

#### 2.1.5 Alcohol

In alcohol drinkers, excessive alcohol consumption should be avoided and intake should not exceed 25 g/day. Drinking in moderation is not a risk factor for coronary heart disease.

### 2.1.6 Influenza Vaccination

Many cohort studies and RCTs have shown that vaccination against influenza reduces cardiovascular morbidity and mortality in patients receiving secondary cardiovascular prevention.[852–855] Developing influenza in winter may influence the progression of cardiovascular disease, including heart failure and ischemic stroke. On the other hand, a significant decrease in cardiovascular morbidity was not observed after vaccination in a relatively young cohort.[852] Thus, annual vaccination is recommended for patients with chronic coronary heart disease, particularly elderly patients.[853–855]

### 2.1.7 Psychological and Social Factors

In patients with myocardial infarction, health-related QOL does not return to the national standard after discharge from hospital, and depressive symptoms are associated with delayed recovery of physical QOL.[856] It has been reported that the risk of recurrent cardiovascular events within 1 year is significantly higher in patients with depressive symptoms after myocardial infarction.[857,858] Therefore, attention should be paid to psychological factors (depression, anxiety, insomnia, etc.), and referral to a psychiatrist or psychologist should be considered as required.

Sufficient education should be provided to the patient and family on an ongoing basis regarding the need to modify the lifestyle, take medications as scheduled, and visit hospital regularly. The social background of patients and their families should also be considered with social support being provided as necessary.

## 2.2 Biomarkers and Genetic Risk Scores

### 2.2.1 Inflammatory Markers

Inflammatory markers are not specific to the cardiovascular system, but many studies have shown that high levels of inflammatory markers, including high-sensitivity C-reactive protein, are independent predictors of restenosis and cardiovascular events, because inflammatory mechanisms are crucially involved in the development and progression of arteriosclerosis and the destabilization and disruption of coronary plaques.[859–861] Because inflammatory markers have been used as surrogate markers in many interventional studies targeting inflammation,[862,863] they are considered to be one of the most important biomarkers for predicting coronary heart disease.

### 2.2.2 Lipid and Myocardial Necrosis Markers

Lipid markers include lipoprotein ratios (LDL-/HDL-cholesterol ratio, etc.), postprandial hyperlipidemia, Lp(a), MDA-LDL, remnant lipoproteins, small-dense LDL, and apoprotein B, all of which have been reported to be associated with arteriosclerotic diseases, including coronary heart disease, and have been utilized clinically. For details, see the 2017 Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases, published by the Japan Atherosclerosis Society.[4]

Creatinine kinase and its MB fraction have conventionally been used as enzymatic markers of myocardial necrosis in clinical practice. However, it has become possible to measure high-sensitivity troponin in recent years, allowing a diagnosis of suspected ACS with a high sensitivity and specificity within a few hours after the onset.[864–867] Clinically, both high-sensitivity troponin T (hs-TnT) and high-sensitivity troponin I (hs-TnI) are used. In a prospective multicenter study of 2,226 patients with suspected non-ST-elevation myocardial infarction,[868] both markers were found to be highly accurate, although hs-TnT was slightly more useful for predicting mortality at 24 months. Elevation of troponin after PCI suggests myocardial damage associated with the procedure, and it has been reported that an elevated troponin level is associated with both the short-term and long-term prognosis.[869–872]

In a cohort study of 2,029 patients with stable coronary heart disease undergoing elective PCI, elevation of hs-TnT (≥14 ng/L) was observed in 527 patients (26%) before PCI and was an independent predictor of 1-year mortality (adjusted hazard ratio: 2.08; 95% CI: 1.10–3.92, P=0.024).[873] Although high-sensitivity troponin is a myocardial-specific biomarker and excellent prognostic indicator in patients with coronary heart disease, specific interventions for patients with elevated troponin levels and the usefulness of troponin as an index of the efficacy of therapeutic intervention have not been established.[874,875]

### 2.2.3 Age- and Sex-Specific Gene Expression Score (ASGES)

ASGES is a risk assessment score that ranges from 1 to 40 and is based on the expression profile of 23 genes determined in peripheral blood leukocytes. In Western countries, it is increasingly accepted as a test that can be used to quantitatively evaluate the risk of coronary heart disease. This risk score correlates with the accuracy of conventional diagnostic procedures such as coronary angiography and CCTA, with a low score indicating low likelihood of coronary heart disease.[876] An ASGES ≤15 has a sensitivity of 89% for detection of coronary heart disease, together with a specificity of 52% and a negative predictive value of 96%.[877] Patients with scores in this range showed no abnormal findings on subsequent stress tests or coronary angiography, and had a low rate of coronary revascularization or major cardiovascular events during 1-year follow-up (1.2% in the ASGES ≤15 group vs. 4.5% in the ASGES >15 group; P=0.03).[878]

The odds ratio for coronary heart disease in the ASGES >15 group compared with the ASGES ≤15 group was 2.5 (95% CI: 1.6–3.8, P<0.001), and the incidence of a composite endpoint of major cardiovascular events was also higher in the former group (adjusted hazard ratio: 1.70; 95% CI: 1.10–2.64, P=0.017).[879] Thus, ASGES is a useful prognostic indicator for prediction of coronary heart disease and cardiovascular events, and is expected to be used clinically as a convenient diagnostic method for coronary heart disease. However, the ability of this score to predict the risk of coronary heart disease has not been clarified in relation to ethnicity and other patient background factors (note: ASGES is not intended for patients with diabetes mellitus), so further research is warranted.

### 2.2.4 Genetic Risk Score

Recent advances in genome-wide association studies have led to the discovery of a number of genetic markers associated with coronary heart disease, including various single-nucleotide polymorphisms, based on which attempts have been made to calculate a genetic risk score for coronary heart disease.[880–882] The score for genetic factors is associated with coronary heart disease independent of conventional risk factors,[883] and it is expected that combining assessment of genetic factors with conventional risk factors, including the family history, may lead to improved prediction of the

**Table 47. Recommendations and Levels of Evidence for Additional Risk Factors and Biomarkers**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Taking a family history | I | B | B | IVa |
| Urate-lowering therapy | IIa | A | B | I |
| CPAP for obstructive sleep apnea | IIa | A | B | II |
| Exercise therapy | I | A | A | I |
| Alcohol intake control | IIa | C | C1 | VI |
| Influenza vaccination | I | B | B | II |
| Consideration of psychological aspects | IIa | C | B | IVa |
| Consideration of social aspects | I | C | C1 | VI |
| Use of inflammatory markers as predictors of coronary heart disease | IIa | B | B | IVa |
| Use of lipid-related/myocardial necrosis markers as predictors of coronary heart disease | IIb | B | C1 | IVa |
| Use of ASGES* as a predictor of coronary heart disease | IIb | C | C1 | IVa |
| Use of genetic risk scores* as a predictor of coronary heart disease | IIb | C | C1 | IVa |

*There is little evidence for the Japanese population, so clinical application may be appropriate in the future. ASGES, Age- and Sex-Specific Gene Expression Score; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

risk of coronary heart disease.[884,885] However, further development of analytical methods, including accumulation of more evidence and obtaining specific data for Japan, is needed before use in the clinical setting will become possible. Recommendations and levels of evidence for additional risk factors and biomarker are shown in **Table 47**.

## 3. Familial Hypercholesterolemia

FH is one of the most common inheritable diseases. It features a triad of elevated LDL-cholesterol (LDL-C), tendinous xanthomas, and coronary atherosclerosis, and FH patients have an increased risk of premature death from early-onset coronary artery disease.[886] FH is also common among patients with coronary heart disease, and a diagnosis of FH is essential for sufficient risk management and for cascade screening of the patient's family.

### 3.1 Clinical Features

#### 3.1.1 Epidemiology

FH is caused by LDL-receptor dysfunction and shows autosomal dominant inheritance, with the exception of rare cases of autosomal recessive hypercholesterolemia (ARH). There are 2 types of FH: heterozygous with 1 causative gene mutation and homozygous with 2 causative gene mutations with severe phenotype. Heterozygous FH were once thought to be a prevalence of 1 in 500 of the general population; however, recent advances in molecular genetics have suggested a much higher prevalence of 1 in 200–300 in many countries, including Japan.[887–889]

As a matter of course, FH is more common among patients with hyperlipidemia or coronary heart disease than among healthy persons. One national survey showed that 3.4% of patients who visited medical institutions because of elevation of LDL-C had FH.[890] Tendinous xanthomas are a highly specific physical finding for FH, and have been reported to be present in approximately 10–20% of patients with ACS in Japan.[891,892] The presence of coronary heart disease per se may be reasonable for a suspicion of FH.

An international study on the diagnosis rate of FH showed that more than 70% of FH patients were diagnosed in the Netherlands, with diagnosis rates generally being high in Europe, while Japan was one of the countries with a very low diagnosis rate of <1%.[887] Improving the diagnosis rate of FH among patients with coronary heart disease is a pressing issue. Although only a few cases of ARH have been reported in Japan, it should be suspected in FH patients without a distinct family history.[893,894]

#### 3.1.2 Hyper-LDL Cholesterolemia

The number of FH gene mutations is related to the cholesterol level, with total cholesterol being 179±26 (mean±SD [mg/dL]) in normal family members of FH patients, 338±63 in heterozygous FH, and 713±122 in FH homozygotes. Thus, the cholesterol level is approximately 2-fold that of normal subjects in heterozygous FH and 4-fold more in homozygous FH (**Figure 19**).[886] A national survey (conducted by the Research Committee on Primary Hyperlipidemia of the Ministry of Health, Labour, and Welfare of Japan) revealed that the mean LDL-C level was 248 mg/dL in 641 untreated FH heterozygotes (296 men and 345 women; mean age: 51 years), showing no sex difference.[895]

Hyper-LDL cholesterolemia is not specific to FH, and there is considerable overlap in the distribution of LDL-C

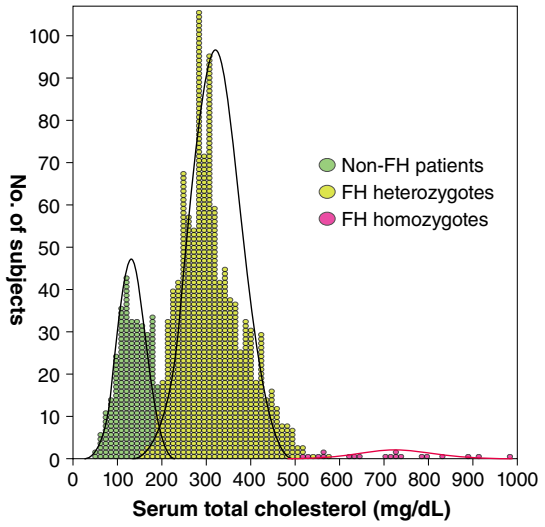



**Figure 19.** Distribution of serum total cholesterol levels in normal subjects, and heterozygous and homozygous patients with FH. (Reproduced from Mabuchi H, 2017,[886] with permission. Copyright (2017) by Japan Atherosclerosis Society. This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License. https://creativecommons.org/licenses/by-nc-sa/4.0/)

**Table 48. Diagnostic Criteria for Heterozygous FH in Adults (15 Years of Age or Older)**

- Hyper-LDL-cholesterolemia (an untreated LDL-C level ≥180 mg/dL)
- Tendon xanthomas (thickening of tendons on dorsal side of the hands, elbows, knees or Achilles tendon hypertrophy) or xanthoma tuberosum
- Family history of FH or premature CAD (within the patient's second-degree relatives)

- The diagnosis should be made after excluding secondary dyslipidemia.
- If a patient meets two or more of the above-mentioned criteria, the condition should be diagnosed as FH. In case of suspected heterozygous FH, making a diagnosis using genetic testing is desirable.
- Xanthelasma is not included in xanthoma tuberosum.
- Achilles tendon hypertrophy is diagnosed if the Achilles tendon thickness is ≥9 mm on X-ray imaging. (See Appendix of the source document.)
- An LDL-C level of ≥250 mg/dL strongly suggests FH.
- If a patient is already receiving drug therapy, the lipid level that led to treatment should be used as the reference for diagnosis.
- Premature CAD is defined as the occurrence of CAD in men <55 years of age or women <65 years of age, respectively.
- If FH is diagnosed, it is preferable to also examine the patient's family members.
- These diagnostic criteria also apply to HoFH.

CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol. (Reproduced from Kinoshita et al 2018,[4] with permission.)

levels between non-FH patients and FH heterozygotes (**Figure 19**). According to the diagnostic criteria of the Japan Atherosclerosis Society (**Table 48**), the threshold LDL-C level is ≥180 mg/dL in adults (≥15 years), based on a balance between sensitivity and specificity.[4] However, the multicenter study for this criterion showed that approximately 5% of FH patients revealed LDL-C <180 mg/dL.[896] Therefore, FH should not be ruled out simply because LDL-C is <180 mg/dL. Mabuchi et al reported that the optimal cutoff LDL-C level for the diagnosis of definite FH was 160 mg/dL based on genetic diagnosis, indicating that FH should be suspected when LDL-C is ≥160 mg/dL in adults.[897] In addition, the LDL-C level is ≥140 mg/dL with a family history of FH in the diagnostic criteria for pediatric FH.[4] Thus, detection of xanthomas and a positive family history are more important for diagnosis of FH than LDL-C, which is less specific.

### 3.1.3 Tendinous Xanthomas, Cutaneous Xanthomas, and Arcus Corneae

#### a. Tendinous Xanthomas

Tendinous xanthomas are pathognomonic for FH and most often affect the Achilles tendon (**Figure 20**).[886,898–900] Tendinous xanthomas are thickenings of tendons due to cholesterol deposits, and FH patients with apparent tendinous xanthomas tend to have more severe coronary artery diease.[901] Although an experienced physician can identify xanthomas by palpation, measuring the Achilles tendon thickness on a lateral X-ray film is quite useful (**Figure 21**).[899,900] Typically, the middle portion that is normally the thinnest part of the Achilles tendon becomes thickened and spindle-shaped, and a width ≥9 mm defined as significant thickening.[901] The Achilles tendon should be measured by carefully determining the distance between the borders of the tendon, not including subcutaneous tissues. Tendinous xanthomas may also develop in the dorsum extensor tendon and elbow joints, so these joints should be flexed to detect the presence of xanthomas (**Figure 20**).[886,898–900]

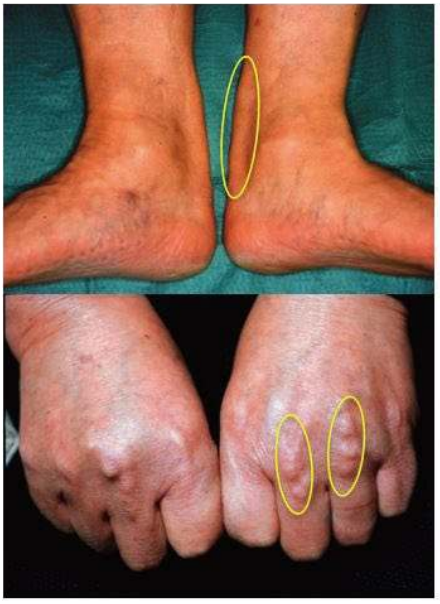
Tendinous xanthomas become more evident with aging. In heterozygous FH, tendinous xanthomas are not found during childhood, but gradually appear from around puberty and finally affect ≈60–70% of patients. From a different point of view, 30–40% of FH patients never develop tendinous xanthomas, even if they remain untreated. Hence, FH cannot be ruled out by the absence of xanthomas. In addition, tendinous xanthomas regress with cholesterol-lowering therapy and are less likely to develop if treated from an early age.

#### b. Cutaneous Xanthomas

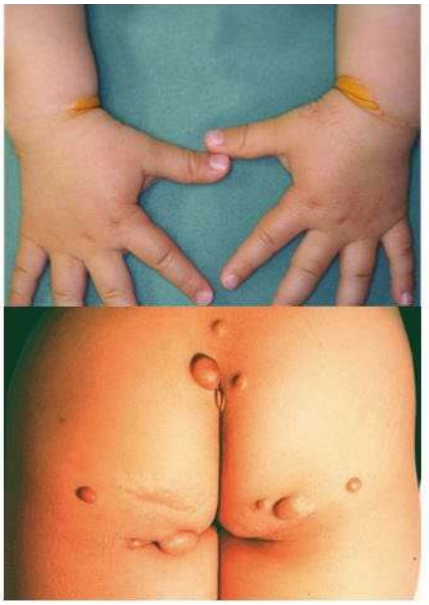
Homozygous FH characteristically develop cutaneous xanthomas during infancy, when tendinous xanthomas are usually absent. Cutaneous xanthomas may also occur during infancy in sitosterolemia,[902] so patients with cutaneous xanthomas should be referred to a lipidologist (**Figure 20**).[886,898–900] It should be noted, however, that palpebral xanthomas (xanthelasma palpebrarum) have a low specificity and are not useful for a diagnosis of FH, because these xanthomas also can be found with normolipidemia.

#### c. Arcus Corneae

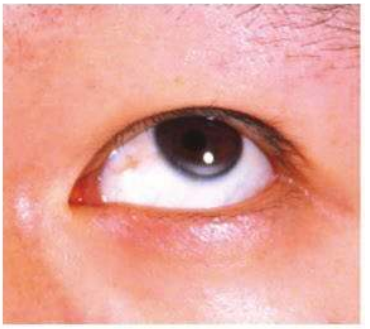
Arcus corneae is found in ≈30% of heterozygous FH under 50 years of age (**Figure 20**).[886,898–900] It initially appears in the 12 o'clock or 6 o'clock direction and may extend to eventually become circumferential. It is difficult to distinguish arcus corneae from arcus senilis, which is common in



**A. Tendinous xanthomas**
Upper: Achilles tendon
Lower: extensor tendons of the hand



**B. Cutaneous xanthomas**
Upper: wrist
Lower: buttocks



**C. Arcus corneae**
6 o'clock direction, lunate

**Figure 20.** Tendinous xanthomas, cutaneous xanthomas, and arcus corneae. (**A**) Tendon xanthomas. Upper: Achilles tendon; Lower: extensor tendons of the hand. (**B**) Cutaneous xanthomas. Upper: wrist; Lower: buttocks. (**C**) Arcus corneae 6 o'clock direction, lunate. (Reproduced from Nohara A, 2017,[900] and Mabuchi H, 2005,[901] with permission.)

elderly persons. However, if a person younger than 50 years old has obvious arcus cornea, it should be considered as a physical finding associated with FH.

### 3.1.4 Early-Onset Coronary Atherosclerosis and Risk of Recurrence

Male FH heterozygotes can develop acute myocardial infarction from around the age of 30 years, whereas female FH heterozygotes do so from around age 50.[886] Before the widespread use of strong statins, 60% of FH patients died of cardiovascular disease. According to Tada et al, CCTA shows development of coronary plaques from ≈20 years of age in male FH patients and from ≈30 years in female FH patients.[903] In an overseas cohort study, Nordestgaard et al reported a 13-fold increase in cardiovascular risk in patients with FH who were not taking statins.[887] Moreover, Mundal et al reported an 8-fold increase in the risk of cardiovascular death in FH patients aged 20–39 years and increased risk of premature mortality,[904] despite the fact that lipid-lowering drugs tend to be prescribed proactively in FH patients. According to Perak et al, the onset of cardiovascular disease was respectively accelerated by 10–20 years in men and 20–30 years in women with FH lipid phenotype.[905] The prognosis of FH patients can be improved by early diagnosis and early initiation of cholesterol-lowering treatment.

Even under secondary prevention of coronary heart disease, FH increases the risk of recurrent events. Nanchen et al reported that the risk of recurrent coronary events during 1 year after hospitalization for ACS was about twice as high in patients with FH than in patients without FH, despite the mean age of the FH patients being at least 10 years younger and use of high-dose statin therapy.[906] In Japan, tendinous xanthomas are found in 10–20% of patients with ACS,[891,892] and such patients should be screened for FH and given appropriate treatment.

## 3.2 Diagnosis

### 3.2.1 Clinical Diagnosis

#### a. Adults

The diagnostic criteria of the Japan Atherosclerosis Society are shown in **Table 48**.[4] Tendinous xanthomas are extremely rare in persons without FH, and FH can be diagnosed if elevation of LDL-C is accompanied by detection of tendinous xanthomas. Because family members may have already died of coronary artery disease, especially in males, a family history of early-onset coronary arteriosclerosis (<55 years for men and <65 years for women) is currently considered to indicate FH among a patient's relatives.[907]

#### b. Homozygous FH

Patients with homozygous FH have a very poor prognosis, because coronary atherosclerosis, supravalvular aortic stenosis, etc. progress from childhood, and cardiovascular death before adulthood is not rare if FH is not sufficiently treated. The clinical diagnosis of homozygous FH is made when both parents are heterozygous FH, the LDL-C level is approximately twice that in heterozygous FH (LDL-C often >500 mg/dL), and cutaneous xanthomas occur from infancy. When homozygous FH is suspected, early referral to a lipidologist should be considered.[908] Homozygous FH

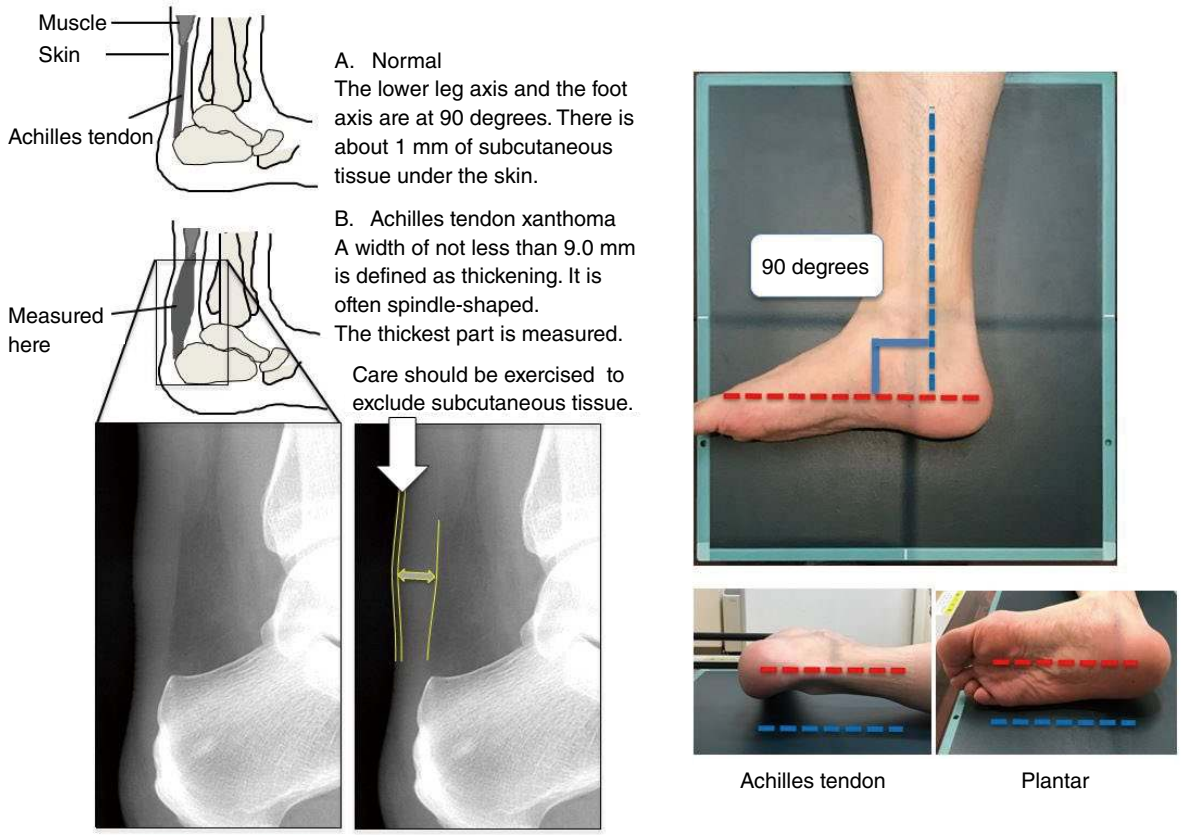



**Figure 21.** Radiographic imaging of an Achilles tendon xanthoma. (Reproduced from Nohara A, 2017,[899] and Mabuchi H, 2005,[900] with permission.)

is under the category of Designated Intractable Diseases covered under the Japanese National Health Insurance system for medical financial support. Genetic diagnosis can be the scientific evidence of diagnosis for the application for subsidies.

### 3.2.2 Genetic Diagnosis

Gene mutations are confirmed in 60–80% of patients with a clinical diagnosis of FH.[886] Mutations of the LDLR gene represent the most common cause of FH. In Japan, ≈5% of FH is caused by mutations of the PCSK9 gene.[886,909] Tada et al reported an additive effect of positive clinical signs such as tendinous xanthoma of FH and positive FH mutation status to coronary artery disease risk among patients with significantly elevated LDL-cholesterol.[910] In addition, APOB gene mutations have been attributed to a significant portion of FH in Caucasians. One allele mutation in the LDLR, PCSK9, or APOB genes causes heterozygous FH as an autosomal dominant pattern of inheritance, and mutations in both alleles in these genes causes homozygous FH. Double heterozygotes with mutations of the LDLR and PCSK9 genes may not show simple Mendelian inheritance. ARH is caused by mutations of the LDLRAP1 gene and shows recessive inheritance, so only homozygotes (or compound heterozygotes) will develop the clinical phenotype of homozygous FH.

In addition, a considerable number of patients who have been considered as severe heterozygous FH with an LDL-C level of ≈400 mg/dL are found to be homozygous by genetic analysis. The genetic diagnosis can provide important information on the potential response to drug therapy, prognosis, and treatment strategies, especially in severe cases. However, genetic diagnosis of FH is not covered by public health insurance at present.

### 3.2.3 Suspected FH

It is important to be aware of the possibility of FH during diagnosis and drug therapy, as it is impossible to make a definite diagnosis for all patients with suspected FH. At present, there is no definition of "suspected FH" in the diagnostic guideline of the Japanese Atherosclerosis Society, but examination and risk management for coronary atherosclerosis should be handled in a similar way to FH, particularly in patients with a family history of hyperlipidemia or coronary artery disease and patients with high LDL-C levels.

### 3.2.4 Differential Diagnosis

#### a. Other Diseases Associated With Xanthomas

In addition to ARH,[893] sitosterolemia[902] can be considered in infants with cutaneous xanthomas and elevation of LDL-C (to the same degree as in homozygous FH) whose parents do not have hyper-LDL cholesterolemia. Cerebrotendinous xanthomatosis can be diagnosed with an elevated

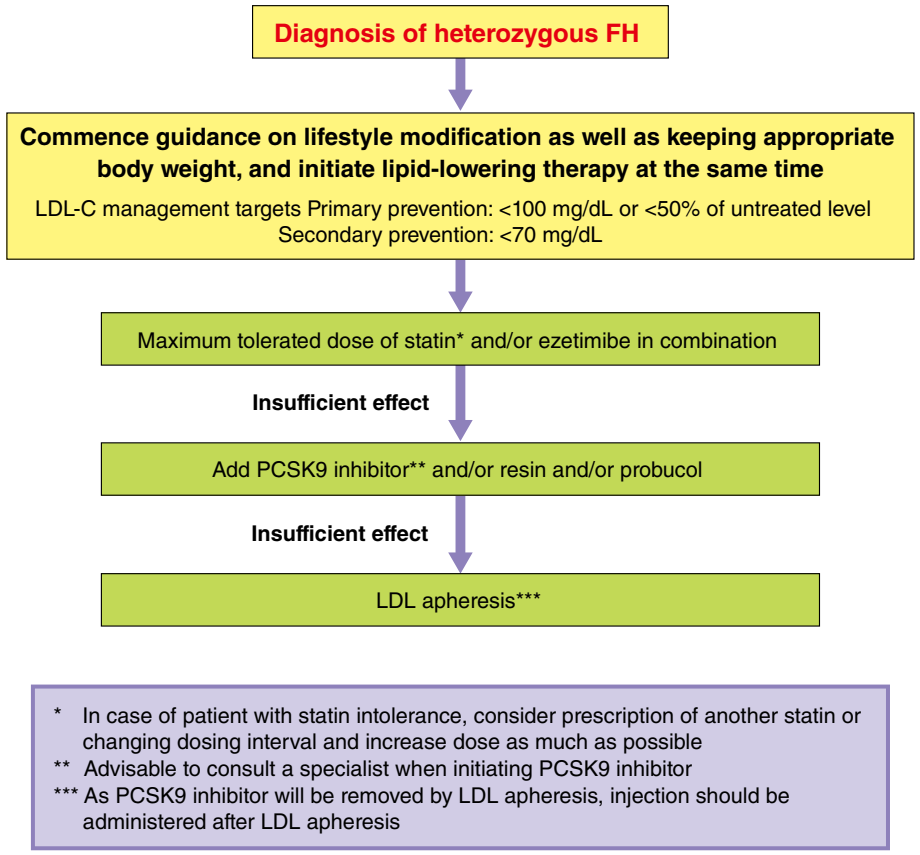



**Figure 22.** Algorithm for treatment of adult (15 years of age or older) FH heterozygotes. LDL-C, low-density lipoprotein cholesterol. (Reproduced from Kinoshita et al, 2018,[4] with permission from the Japan Atherosclerosis Society. https://www.jstage.jst.go.jp/article/jat/25/9/25_GL2017/_pdf/-char/en)

plasma cholestanol level and prominent tendinous xanthomas disproportionate to the LDL-C level.[911]

## 3.3 Lipid Management

### 3.3.1 Lipid Management Targets for Primary and Secondary Prevention

FH is a high-risk disease for coronary heart disease, and lipid-lowering therapy should be started at the same time as guidance on lifestyle modification and optimum body weight (**Figure 22**).[912] The target LDL-C level is <100 mg/dL or <50% of the untreated LDL-C level for heterozygous FH as primary prevention therapy, and is <70 mg/dL for both heterozygotes and homozygotes in secondary prevention therapy. As dietary therapy for FH, patients should be instructed as follows: (1) keep the intake of saturated fatty acids from 4.5% to 7%, (2) reduce the intake of trans-fatty acids, and (3) keep cholesterol intake to ≤200 mg/day.

### 3.3.2 Selection of Drugs

Statins are the first-line drug therapy, and efficacy of statin therapy for preventing cardiovascular events in FH patients has been reported in Japan and overseas.[913,914] Strong statins should be used, together with ezetimibe, resins (bile acid sequestrants), etc., but it is often difficult to maintain LDL-C <70 mg/dL in FH patients for secondary prevention. PCSK9 inhibitors can further reduce LDL-C levels by ≈60% in FH heterozygotes already on treatment with existing therapies such as statins, and reduce Lp(a) as well.[915,916] The FOURIER study of patients with a high risk of coronary heart disease showed that evolocumab reduced cardiovascular events.[817] In the ODYSSEY OUTCOME study investigating post-ACS patients, alirocumab reduced cardiovascular events and all-cause death. From the perspective of medical economics, PCSK9 inhibitors should be indicated for FH patients for the secondary prevention of coronary heart disease who show an insufficient response to the maximum tolerable doses of statins combined with ezetimibe.[917]

#### a. Treatment Algorithm for Heterozygous FH

Strong-statin-based therapy should be initiated, combined with ezetimibe as needed, and additional drugs may be considered if the response to these medications is insufficient.[4,912] Particularly, PCSK9 inhibitors should be considered when necessary, especially for FH patients in secondary prevention (**Figure 22**).[917] LDL-apheresis may also be considered in the secondary prevention for patients who do not respond sufficiently to PCSK9 inhibitors. However, homozygous FH should be suspected in such patients

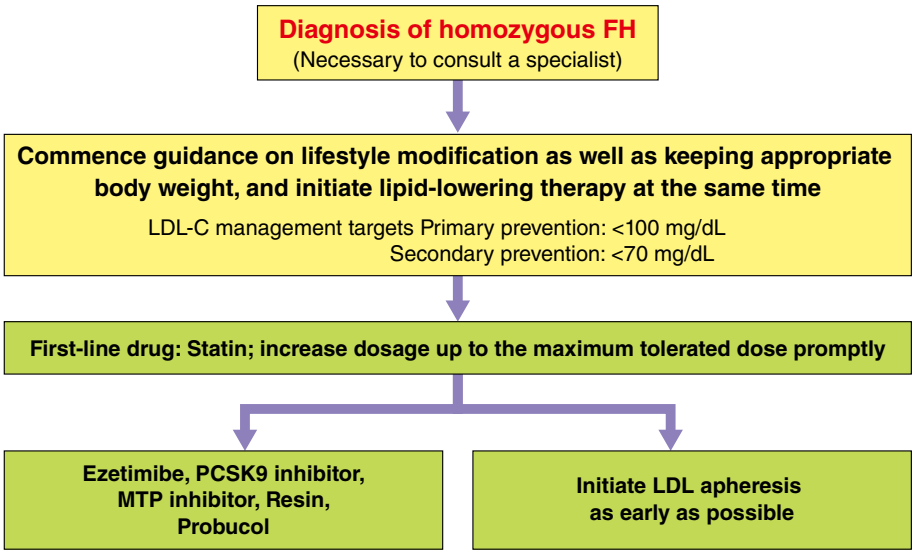



**Figure 23.** Algorithm for treatment of adult (15 years of age or older) FH homozygotes. LDL-C, low-density lipoprotein cholesterol. (Reproduced from Kinoshita et al 2018,[4] with permission from the Japan Atherosclerosis Society. https://www.jstage.jst.go.jp/article/jat/25/9/25_GL2017/_pdf/-char/en)

**Table 49. Recommendations and Levels of Evidence for FH**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| FH should be suspected in patients with premature coronary heart diseaase (men <55 years old and women <65 years old) | I | C | A | IVb |
| Presence of tendinous xanthomas should be checked in all patients with coronary heart disease | IIa | C | B | IVa |
| High-intensity statins are the first choice for LDL-C-lowering therapy in FH, and combination with ezetimibe should be considered when required | I | C | A | VI |
| In secondary prevention for patients with FH, an LDL-C goal of <70 mg/dL is recommended, and appropriate combination therapy should be considered when necessary | IIa | C | B | VI |
| If FH is diagnosed, it is preferable to also examine the patient's family members | I | C | B | VI |

COR, class of recommendation; GOR, grade of recommendation; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence.

and genetic diagnosis should be strongly considered.

### b. Treatment Algorithm for Homozygous FH

The prognosis is poor and if the response to current treatment is insufficient, more aggressive treatment should be considered (**Figure 23**). Statins and PCSK9 inhibitors are dependent on LDL-receptor activity and are often less effective or ineffective for homozygous FH. The degree of LDL-C reduction with these drugs can be achieved according to the residual LDL-receptor activity.

LDL-apheresis is still a mainstay of treatment for homozygous FH. These patients should be managed by combining multiple active treatments. MTP inhibitors are oral drugs that work independent of LDL-receptor activity. Only homozygous FH patients are indicated for MTP inhibitor therapy, which can reduce LDL-C levels by half. However, gastrointestinal symptoms and hepatosteatosis are common side effects, so MTP inhibitors should be started at a low dose under the guidance of a specialist, together with dietary counseling and restriction of alcohol intake.[918]

## 3.4 Diagnosis and Treatment of Family Members

An early diagnosis and treatment are essential to prevent premature death in FH patients, but the diagnosis rate is extremely low in Japan.[887] Therefore, many undiagnosed cases are suspected to exist in a family with FH. In fact, there is a 50% chance that parents and siblings may have FH. Accordingly, when a diagnosis of FH is made, the physician should also advocate testing and treatment for family members.

## 3.5 Future Challenges

More aggressive lipid-lowering therapy is required for FH

patients than for non-FH patients, and it is particularly important to sufficiently reduce the LDL-C level in secondary prevention. In patients with chronic coronary heart disease, it is important to diagnose and treat FH adequately, together with an early diagnosis and treatment of family members. Recommendation and levels of evidence for diagnosis of FH are shown in **Table 49**.

# III. Selecting Tests for Chronic Coronary Heart Disease Based on the Pathological Condition and Diagnostic Objectives

## 1. Diagnosis of Myocardial Ischemia

Investigation of myocardial ischemia is essential for diagnosing and assessing the severity of chronic coronary heart disease. Making a choice from among pharmacological therapy, PCI, or CABG requires quantitative assessment of regional myocardial ischemia, rather than anatomical coronary artery stenosis. Stress testing is usually done to detect the existence of myocardial ischemia, except when it is contraindicated. Exercise stress ECG is widely used for noninvasive testing, because it is simple and cost-effective and can evaluate the severity of ischemia, exercise tolerance, and the prognosis. However, exercise stress ECG does not always have a high sensitivity and specificity for diagnosing the culprit vessels causing ischemia and the ischemic regions.

Accordingly, stress myocardial perfusion imaging and stress echocardiography are used when exercise cannot be performed or when diagnosing ischemia by ECG is found to be difficult. In recent years, the use of CCTA has been increasing rapidly. In high-risk patients who are considered to have severe myocardial ischemia based on symptoms and the results of noninvasive testing, coronary angiography should be performed in anticipation of coronary revascularization. Coronary angiography is invasive, but essential to confirm the diagnosis of coronary heart disease and determine the need for revascularization.

Whether coronary angiography is performed should be decided by comprehensive assessment of the clinical findings, laboratory findings, and the patient's wishes. The prevalence of patients with vasospastic angina is higher in Japan than in Western countries, and the pathophysiology of this condition differs from that of effort angina. Therefore, performing Holter ECG and coronary spasm provocation testing are required for diagnosis.

It is desirable to select the most appropriate examination from among various modalities for evaluating myocardial ischemia, according to the purpose. The diagnostic algorithm for myocardial ischemia (**Figure 24**) is set out below. For the details of each test, see the relevant sections of this Guideline. With regard to FFR-CT, HeartFlow FFR-CT has been covered by health insurance in Japan as of December 2018. However, the number of facilities that can perform this test is limited and further evidence needs to be accumulated. Accordingly, FFR-CT has not been included in the algorithm.

### 1.1 Initial Assessment of Clinical Findings

It is important to estimate the probability of the existence of coronary heart disease (pretest probability) from clinical findings such as the patient's history and coronary risk factors.[510]

#### 1.1.1 History

Taking an accurate history is the most important starting point for the diagnosis of angina pectoris. The history is also important for understanding the patient's social background and personality, establishing a relationship of trust with the patient, and obtaining informed consent.

##### a. Symptoms

Information should be collected about the site, nature, duration, onset, and offset of chest symptoms (pain, etc.), as well as associated symptoms.[919] The sites of symptoms include the mid-precordial region, left anterior chest, and epigastrium, with the most common site being the mid-precordial region. Symptoms generally affect an appreciable area, so localized symptoms such as those indicated by a single finger are unlikely to be due to coronary heart disease. Symptoms often radiate to the neck, throat, jaw, arms, shoulders, and back, and may also be confined to any of these areas. Patients often describe a feeling of oppression, squeezing, or leadenness, and shortness of breath may be the chief complaint of patients with severe ischemia. A sharp pain, commonly described as tingling or throbbing, is unlikely to be related to coronary heart disease.

The duration of symptoms is often a few minutes or less, and symptoms may be induced by physical exertion, mental agitation, cold exposure, etc. If provoked by exertion, symptoms resolve within minutes of stopping exertion and use of a rapid-acting nitrate preparation. Women, elderly persons, and patients with diabetes mellitus often have atypical symptoms. Also, elderly persons, patients with diabetes mellitus, patients with a history of myocardial infarction, and patients who have undergone surgical coronary revascularization tend to have asymptomatic myocardial ischemia. Therefore, history taking should be done carefully for these patients.[920]

##### b. Medical History and Oral Medications

Information should be collected about the presence and management of diabetes mellitus, hypertension, and dyslipidemia, the presence/absence of smoking (current or prior), a family history of coronary heart disease, and oral medications. See Chapter II of this Guideline for details of these coronary risk factors.

#### 1.1.2 Physical Findings

Physical findings are not noteworthy in many patients. In patients with severe ischemia, however, a gallop rhythm or systolic regurgitant murmur may be audible by auscultation during attacks because of decreased left ventricular wall motion and mitral regurgitation. Physical findings are important for differentiation from other diseases that can cause thoracic symptoms (pericardial disease, heart failure, pulmonary/pleural disease, pulmonary embolism, gastrointestinal disease, musculoskeletal disease, etc.).

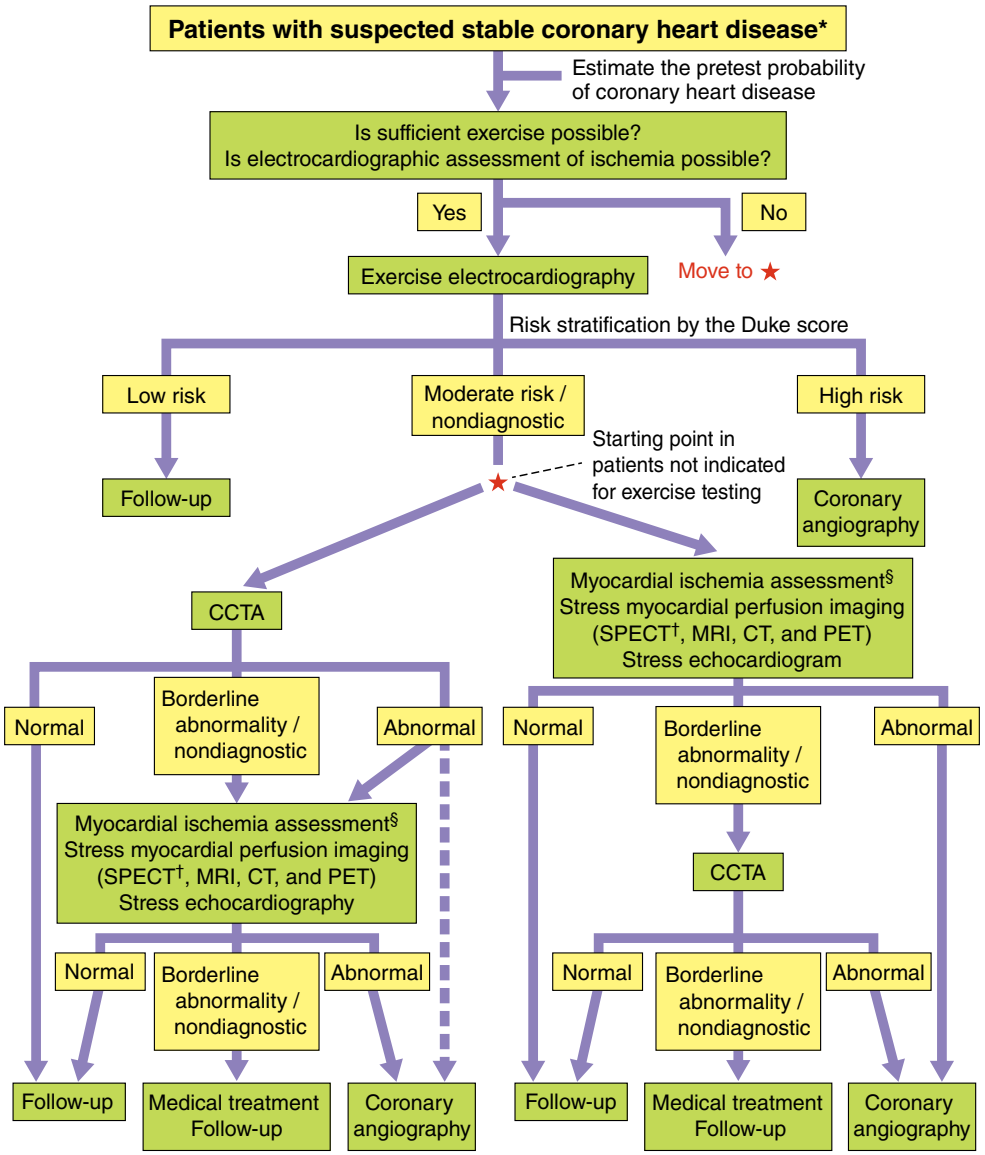



**Figure 24.** Diagnostic algorithm for myocardial ischemia. *This also applies to asymptomatic patients strongly suspected to have coronary heart disease based on electrocardiography, echocardiography, etc. Dashed arrow: coronary angiography should be performed when a severe stenosis clearly indicated for coronary revascularization is observed. †Exercise stress myocardial scintigraphy should be performed if exercise is possible; otherwise, pharmacological stress myocardial scintigraphy is done. §FFR-CT may be useful for assessment of myocardial ischemia, but there are only limited facilities where it is covered by health insurance as of December 2018. Note: when selecting tests, due consideration should be given to contraindications, as well as the risks and side effects.

### 1.1.3 Standard 12-Lead ECG

Standard 12-lead ECG is the most convenient and basic diagnostic test for coronary heart disease in daily clinical practice. In patients with angina symptoms or having an angina attack, 12-lead ECG should be recorded. However, the ECG may be normal during the intervals between angina attacks in patients with stable angina. Therefore, coronary heart disease cannot be ruled out by a normal resting ECG in these patients.[921]

The diagnosis of myocardial ischemia is mainly based on detection of ST-T changes. However, the ST-segment and T wave can be affected by a wide range of conditions, including cardiac hypertrophy, intraventricular conduction defects, myocardial disease, electrolyte abnormalities, drugs such as digitalis preparations, and autonomic activity.[922,923] Differentiation between changes caused by these conditions and myocardial ischemia is often difficult and requires comprehensive assessment of the history, clinical findings, and other laboratory results.

#### a. ST Elevation

ST elevation suggests transmural ischemia caused by complete occlusion of the culprit coronary artery,[922] and ST elevation is observed in leads facing the site of transmural

ischemia. However, ST elevation can also be seen as an electrocardiographic finding in normal individuals. The normal ST level varies with age, sex, and the ECG leads. In general, it is highest in leads V2–3, and higher in men than in women.[924] According to an international definition,[922] ST elevation is electrocardiographic evidence of acute myocardial ischemia if it occurs in ≥2 contiguous leads and has the following characteristics: ST elevation ≥0.20 mV in leads V2–3 in men aged 40 years or older; ST elevation ≥0.25 mV in leads V2–3 in men under 40 years old; ST elevation ≥0.15 mV in leads V2–3 in women of any age; or ST elevation ≥0.1 mV in leads other than V2–3. (This definition applies in the absence of left ventricular hypertrophy or left bundle branch block, and the ST level is measured at the J point.)

#### b. ST Depression

ST depression is the most important electrocardiographic evidence of subendocardial ischemia. However, it is difficult to diagnose the culprit vessel on the basis of ST depression (unlike ST elevation), because ST depression generally occurs in leads V4–6 regardless of the culprit coronary artery. The extent of myocardial ischemia increases as ST depression becomes deeper, involves a larger number of leads, or becomes longer.

In daily clinical practice, an ECG diagnosis is often done by using 11 leads and excluding aVR. However, aVR is a useful lead for the diagnosis of extensive ischemia of the left ventricular endocardium because it looks into the left ventricular cavity from the right shoulder. Severe ischemia because of left main trunk disease or multivessel disease can be suspected in the case of ST elevation in lead aVR combined with widespread ST depression.[925]

#### c. Negative T Wave

Negative T waves are considered to reflect abnormal repolarization of the ischemic myocardium and are a representative electrocardiographic finding together with ST depression.

#### d. Negative U Wave

Negative U waves are a highly specific electrocardiographic finding that suggests severe myocardial ischemia when they occur transiently during an ischemic attack or during exercise testing, and thus have high diagnostic significance. Negative U waves occur in leads facing the site of ischemia, and negative U waves centered on leads V3–5 suggest a left anterior descending artery lesion.[926] Because the negative U wave is a shallow and small wave following the T wave, it is important to form a diagnosis by keeping in mind that negative U waves may appear at the time of ischemia. On the other hand, negative U waves can be observed when the blood pressure is elevated or in patients with conditions such as aortic valve regurgitation. Hence, a diagnosis of myocardial ischemia should be made in consideration of other clinical findings.

#### e. Abnormal Q Wave

The presence of abnormal Q waves contributes to a diagnosis of myocardial infarction.[922] However, because isolated Q waves in lead III and a QS patterns in lead V1 may be seen in normal persons,[922] the diagnosis must be made in conjunction with the history, clinical findings, and other laboratory results.

### 1.1.4 Chest X-ray

Chest X-ray findings are often normal in patients with stable angina. However, abnormalities may be detected in patients with a history of myocardial infarction, patients with other types of heart disease, or patients with pulmonary/pleural disease or skeletal disease who complain of chest symptoms attributable to causes other than coronary heart disease. An enlarged cardiac silhouette suggests a history of myocardial infarction, as well as heart failure, valvular disease, and pericardial effusion. The presence of pulmonary congestion is also an important finding in the diagnosis of severe ischemia.

## 1.2 Selection of Examination Tests

It is crucial to estimate the pretest probability of coronary heart disease, to select diagnostic tests based on this, and to plan the next diagnostic strategy from the results thus obtained. Stress testing is performed to induce myocardial ischemia and to examine its presence and extent. However, stress testing is contraindicated in patients with ACS in principle, and patients must be monitored for changes in symptoms or resting ECG findings at the time of appointment or before testing.

### 1.2.1 Exercise ECG

Exercise ECG is widely used for the diagnosis of myocardial ischemia because it is simple, cost-effective, and allows both assessment of exercise tolerance and evaluation of the prognosis. However, there are some limitations to its indications because patients must be able to perform exercise and because the diagnosis of ischemia on the ECG must be possible, including the absence of conditions causing ST-T abnormalities on the resting ECG such as Wolff-Parkinson-White (WPW) syndrome or left bundle branch block. It is important to keep the pretest probability in mind when making a diagnosis.

For elderly men who have multiple coronary risk factors and typical clinical features of effort angina, exercise testing with continuous recording of the ECG and blood pressure monitoring is recommended. If the test is positive, there is a high probability that the patient has coronary heart disease (true-positive result). If the test is negative, the possibility of a false-negative result should be considered. In contrast, young and middle-aged adults often have normal coronary arteries even when the exercise ECG shows abnormalities (false-positive result).[927] Thus, diagnosis of ischemia should be made by comprehensive assessment, and not solely from the exercise ECG.[928]

Exercise testing is not only useful for diagnosing myocardial ischemia, but also for estimation of the prognosis. A larger number of lesions, higher frequency of ST depression, ST depression ≥0.2 mV, onset of ST depression at a low exercise load, poor blood pressure response to exercise, and poor exercise tolerance are all negative prognostic indicators.[5,28,30,31,929,930] When treadmill exercise ECG is performed, risk stratification is possible by calculating the Duke treadmill score from the duration of exercise loading, maximum ST depression, and chest symptoms as follows: (exercise duration) − 5×(maximum ST depression in mm) − 4×(angina pectoris score: 0 for no angina symptoms during stress testing, 1 for angina symptoms, and 2 if angina symptoms require cessation of exercise). A score of −11 or less is considered to indicate a high risk, while a score of +5 or more is considered to indicate a low risk.[5] If

the risk is low, the prognosis is good and only routine follow-up is required. If the risk is judged to be high, coronary revascularization should be considered and coronary angiography is a priority. If the risk is intermediate or undeterminable, another noninvasive test should be selected for achieving a diagnosis.

Exercise ECG is the noninvasive test of first choice for myocardial ischemia, but it has several limitations. In particular, nonspecific ST depression (≥0.1 mV) on the resting ECG, cardiac hypertrophy, intracardiac conduction abnormalities (bundle branch block, ventricular pacing, WPW syndrome, etc.), use of digitalis preparations, electrolyte abnormalities, and a history of myocardial infarction are known to render this test nondiagnostic (i.e., the result is often undeterminable, or else false-positive or false-negative). Accordingly, other tests should be selected when it is difficult to diagnose ischemia by ECG or if exercise is considered to be contraindicated or inappropriate (elderly patients, patients with aneurysms, PAD, etc.). For the performance of exercise ECG, see the sections describing the individual methods in this Guideline.

### 1.2.2 Selection of Other Noninvasive Tests

Noninvasive tests that may follow or replace exercise ECG include stress echocardiography,[931–933] which can evaluate physiologic and functional myocardial ischemia, and stress myocardial perfusion imaging modalities such as stress myocardial perfusion scintigraphy, MRI, CT, or PET[226,227,262,265,300,934–938] These tests have a high level of diagnostic usefulness when the pretest probability (mentioned above) is considered to be intermediate. The advantages of stress echocardiography over stress myocardial perfusion imaging are that it is simple and does not require expensive equipment, large facilities, or radiopharmaceuticals for which particular caution needs to be exercised. Disadvantages include the difficulty of recording good images in some patients and high dependency of the results on the skill of the operator. On the other hand, stress myocardial perfusion scintigraphy shows high diagnostic accuracy for evaluation of myocardial ischemia without needing contrast medium, and is therefore widely used in daily clinical practice. In addition to the presence of myocardial ischemia, the extent and severity of myocardial ischemia can be examined, and there is abundant evidence for its use in prognostic evaluation.[226,227,262,400,934–936]

However, it is a relative method of evaluation based on the difference in blood flow between normal and ischemic myocardium, so there are limitations for detecting ischemia in patients with severe and extensive myocardial ischemia, such as those with multivessel disease or left main trunk lesions. Other disadvantages are relatively high radiation exposure and low image resolution, making it impossible to perform a morphological evaluation of the coronary arteries. Stress myocardial perfusion imaging with PET achieves superior image quality to SPECT, but it is only covered by health insurance for diagnosis of myocardial ischemia that is difficult to determine by other modalities. The radionuclide used for myocardial perfusion PET is N-13 ammonia, which has a short half-life of 10 min and is only available at a limited number of facilities where it can be synthesized. On the other hand, stress myocardial perfusion MRI does not involve radiation exposure and has a high spatial resolution allowing clear delineation of subendocardial ischemia and diffuse myocardial ischemia caused by multivessel disease.

It has been reported to show better diagnostic performance than stress myocardial perfusion scintigraphy.[265,597] However, it is not widely used because of problems such as the complexity of the test, long imaging time, and high level of skill required for interpretation. CCTA has high accuracy for detecting coronary artery stenosis[939–941] and can be performed rapidly with low invasiveness, so there has been a dramatic increase in its use in recent years. In addition, CT stress myocardial perfusion imaging can be done to assess myocardial ischemia by observing contrast staining of the myocardium after drug administration. It has been reported to be useful as an auxiliary method for the diagnosis of lesions that cannot be evaluated on CCTA and lesions with moderate or severe stenosis, because it has a similar diagnostic performance to SPECT or MRI for detecting stenotic vessels and myocardial ischemia. Thus, the noninvasive tests that can follow or replace exercise ECG are morphological evaluation with CCTA, stress myocardial perfusion imaging (SPECT, MRI, CT, and PET), or stress echocardiography to evaluate myocardial ischemia.

The choice of modality will depend on the estimated pretest probability for coronary heart disease, the institution (whether the diagnostic accuracy of a given test is adequate at each institution), and the patient (is the test sufficiently indicated in a given patient). Regarding the patient, adequate consideration should be given to contraindications and the risks/side effects of testing. Noninvasive diagnosis of myocardial ischemia is important when determining the indications for invasive coronary angiography and coronary revascularization, and evaluation of myocardial ischemia by stress myocardial perfusion SPECT is well documented and it is often the method of first choice.

In the case of stress myocardial perfusion scintigraphy showing that coronary artery stenosis is not functionally significant, the prognosis is good and the patient is followed up routinely. Performing CCTA may be considered if mild perfusion abnormalities are present or if the result is undeterminable. On the other hand, moderate or severe abnormalities on stress myocardial perfusion scintigraphy indicate a high risk, so coronary angiography should be performed in anticipation of coronary revascularization.

CCTA has a high negative predictive value and is excellent for exclusion diagnosis.[941] If CCTA gives a normal result, coronary artery disease can be almost completely ruled out and the patient should be followed up. Even if CCTA shows mild abnormalities, the patient should be followed up because myocardial ischemia is unlikely. If significant stenosis is detected, CCTA only provides an anatomical assessment, so whether coronary revascularization is required should be determined by other diagnostic methods that can confirm the presence of myocardial ischemia. Nevertheless, if a severe stenosis is found that seems clearly indicated for coronary revascularization, coronary angiography should be performed next. On the other hand, when judgment by CCTA is difficult because of severe calcification, motion artifacts, borderline stenosis, etc., myocardial ischemia can be assessed by other modalities. More recently, fusion imaging with CCTA and myocardial blood flow SPECT have been developed, allowing simple and accurate detection of the culprit coronary artery by utilizing the advantages of morphological and functional imaging;[942] improvements in both are expected in the future. See the sections describing the individual tests in this Guideline for details of each test.

**Table 50. Recommendations and Levels of Evidence for Testing Methods to Assess Myocardial Ischemia in Patients With Suspected Stable Coronary Heart Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Exercise testing in patients who can perform exercise and can undergo ECG assessment of ischemia | I | B | C1 | IVb |
| Stress imaging in patients who cannot perform exercise or undergo ECGassessment of ischemia | I | B | C1 | IVb |
| CCTA in patients who cannot perform exercise or undergo ECG assessment of ischemia | IIa | C | C1 | VI |
| Coronary angiography in patients clinically judged to be low risk who have not undergone noninvasive assessment of ischemia | III | C | C2 | VI |

CCTA, coronary computed tomography angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

## 1.3 Diagnosis of Myocardial Ischemia in Patients With Vasospastic Angina

Vasospastic angina is more common among Japanese patients than in Westerners.[63] Because the mechanisms underlying onset, pathology, and clinical features differ between vasospastic angina and stable effort angina, the methods used for diagnosis of myocardial ischemia are also different. In patients with stable effort angina, significant coronary stenosis exists and causes myocardial oxygen demand to exceed oxygen supply on exertion, giving rise to myocardial ischemia. Therefore, exercise testing is useful for diagnosis of myocardial ischemia in these patients. On the other hand, coronary blood flow is decreased by functional coronary artery occlusion or stenosis stemming from coronary spasm in patients with vasospastic angina, resulting in myocardial ischemia. Vasospastic angina often occurs at night or in the early morning. Therefore, its diagnosis requires Holter ECG and a coronary spasm provocation test. The detailed diagnosis of vasospastic angina has been described in the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina (revised in 2013),[63] so this section provides brief information.

### 1.3.1 Symptoms

Although the symptoms do not differ from those of effort angina, an attack of vasospastic angina has the following characteristics: (1) particularly occurs while resting at night or in the early morning (often during sleep) and is not usually induced by daytime exercise, but can be induced by mild exertion in the early morning, so there is clear diurnal variation; (2) may be induced by hyperventilation or alcohol; (3) rapid-acting nitrates are highly effective for controlling attacks and calcium antagonists are effective for prevention; and (4) attacks are often accompanied by arrhythmias and disturbance of consciousness or loss of consciousness may occur if there is associated complete atrioventricular block, ventricular tachycardia, or ventricular fibrillation.[943]

### 1.3.2 Standard 12-Lead ECG

ECG is often normal in the absence of an attack. However, a definitive diagnosis can be made by recording and comparing 12-lead ECGs during an attack and in the normal state. The most typical electrocardiographic finding during an attack is ST elevation in the leads facing the site of coronary spasm,[944] whereas negative T waves are often seen as the myocardium is recovering from ischemia. However, electrocardiographic changes depend on the severity of coronary spasm and may include ST depression or appearance of new negative U waves.[945]

### 1.3.3 Holter ECG

About 20–30% of patients with vasospastic angina have chest symptoms associated with ST changes and asymptomatic coronary spasm is common. Because attacks often occur while resting at night or in the early morning and are sometimes associated with arrhythmias, Holter ECG is a highly useful diagnostic test.[63] Multichannel or 12-lead Holter ECG should be recorded rather than 2-channel ECG whenever possible. The possibility of capturing the electrocardiographic changes during an attack increases as the recording time becomes longer.

### 1.3.4 Coronary Spasm Provocation Testing

The major methods of inducing coronary spasm are noninvasive hyperventilation (breathing at a rate of approximately 30 breaths/min for several minutes)[946,947] and invasive pharmacological stress testing, which requires intracoronary infusion of acetylcholine[653,667,948] or ergonovine[656,657] using cardiac catheterization. Sufficient consideration is required when performing a coronary spasm provocation test, especially in patients at risk of syncope or severe arrhythmia. See the relevant sections of this Guideline for more details.

### 1.3.5 Diagnostic Algorithm

For a diagnosis of vasospastic angina, refer to the diagnostic algorithm in the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina (revised in 2013).[63] Recommendations and levels of evidence for diagnosis of myocardial ischemia are shown in **Table 50**.

## 2. Assessment of Coronary Artery Lesions

Assessment of coronary artery lesions is important for the diagnosis, treatment, and prognostication of coronary heart disease. When coronary angiography was the gold standard, it was important to morphologically or functionally assess the severity of coronary artery stenosis. However, it has become clear that vulnerable plaques, which cause ACS and determine the prognosis of coronary heart disease, exist irrespective of the severity of stenosis. Thus, it is important not only to evaluate ischemia but also to identify vulnerable plaques. Because coronary angiography cannot identify vulnerable plaques, intravascular imaging modalities such as IVUS, OCT[949] and angioscopy are required to

detect vulnerable plaques, as well as providing more accurate morphological assessment of coronary artery stenosis. On the other hand, the diagnostic accuracy of noninvasive MDCT and whole-heart MRA for coronary artery lesions has improved, and morphological information can now be obtained with these modalities, including not only the extent of stenosis but also the presence and properties of plaques. Assessment of ischemia is also important when deciding the treatment of chronic coronary heart disease. Although coronary angiography is still gold standard for assessing stenotic lesions, noninvasive assessment of functional ischemia using Doppler echocardiography or MRI, or alternatively invasive assessment with a Doppler guidewire or pressure guidewire, is required in addition to morphological assessment. Because there is no optimum method at present, it is not desirable to evaluate coronary artery stenosis based on a single method and other evidence of ischemia should also be considered.

Coronary heart disease causes angina pectoris or myocardial infarction due to gradual progression of arteriosclerosis over many years, as well as to rapid formation of thrombi on arteriosclerotic plaques. Progression of coronary artery lesions may not always coincide with the onset of symptoms. Even if coronary artery stenosis progresses, the coronary arteries have an autoregulatory mechanism that may still provide adequate blood flow to meet demand. Thus, angina symptoms only appear after progression of stenosis is severe enough to cause failure of this mechanism.[950] It has been demonstrated that myocardial infarction can also be caused by lesions without severe stenosis.[951,952] Although there is thus some discordance between symptoms and lesion severity, assessment of coronary artery stenosis is essential to clarify whether symptoms are actually due to coronary heart disease, to determine the severity of the disease, and to select the treatment strategy, including revascularization.

After selective coronary angiography was developed,[637,638] coronary angiography became the gold standard for investigation of coronary artery stenosis. Currently, it is also possible to evaluate the degree of coronary artery stenosis by noninvasive tests such as MDCT, echocardiography, and MRI. Regarding other invasive tests, the process of vascular remodeling (in which the vessel diameter expands to preserve the intravascular lumen as plaque grows inside the vessel because of arteriosclerosis) has been clarified by advances in intravascular imaging,[953] whereas coronary angiography only evaluates the intravascular lumen and cannot assess such changes.[954] In addition, direct observation of arteriosclerosis lesions by IVUS, OCT, and angioscopy enables determination of the nature of lesions and prediction of ACS. In patients with moderate stenosis whose symptoms cannot be explained by morphological assessment of stenosis, a Doppler guidewire[764] or pressure guidewire[568] can be used to evaluate functional coronary artery stenosis.

## 2.1 Assessment of Coronary Artery Lesions in Chronic Coronary Heart Disease

In patients who have stable effort angina or asymptomatic myocardial ischemia,[955,956] ischemic changes arise from exertion, irrespective of whether these changes are symptomatic or asymptomatic. This section describes the methods for evaluating coronary artery lesions in patients with stable chronic coronary heart disease.

### 2.1.1 Targets for Evaluation

In patients with stable symptoms, objective indicators of myocardial ischemia include ischemic ST-T changes on stress ECG, decreased wall motion on stress echocardiography, and decreased blood flow on myocardial perfusion imaging. As the next step, evaluation of coronary artery stenosis is required.

### 2.1.2 Noninvasive Evaluation

#### a. CCTA

MDCT has improved the spatial and temporal resolution of CT scans, and the current mainstream 64-row MDCT can be used for definitive diagnosis of coronary heart disease.[957] At present, 320-row MDCT is also available, and equipment with even more improved spatial resolution is being developed.[2] MDCT can be used to assess coronary artery stenosis, patency of coronary stents, or patency of coronary artery bypass grafts and the vessel beyond the anastomosis.[958] It also allows detection of noncalcified coronary artery plaques[959] and assessment of coronary artery remodeling.[960] However, although radiation exposure has been reduced with advances in equipment, it is still problematic to use CCTA for screening.[957]

**i) Evaluation of Lesions**

Comparison of 64-row MDCT with coronary angiography (gold standard) for detection of significant coronary artery stenosis showed a sensitivity of 82% and 99%, specificity of 64% and 91%, positive predictive value of 64% and 92%, and negative predictive value of 81% and 99%, respectively.[941,961,962] Because MDCT has a high negative predictive value, it is particularly useful for exclusion diagnosis, such as when symptoms are atypical.[618,957,963] However, a meta-analysis of randomized studies comparing CCTA and exercise testing in patients with suspected coronary heart disease showed that myocardial infarction was decreased in patients undergoing CCTA, but performance of PCI was increased, with no decrease in hospitalization or death.[940]

Unlike coronary angiography, CCTA can visualize the vessel wall and adjacent tissues, enabling preoperative characterization of the lesion. Even if there is total occlusion, visualization of collateral vessels and the course of the occluded vessel is possible, allowing estimation of the feasibility and likely success rate of treatment.[964] In patients with coronary stents, stent fracture can be visualized, in addition to assessment of the lumen.[965] It has recently become possible to evaluate functional coronary artery stenosis with MDCT by calculating the FFR-CT,[939] providing high diagnostic accuracy for the diagnosis of significant CAD, compared with invasive FFR as the reference standard.[560] However, FFR-CT cannot be calculated if a coronary artery has been stented. Among the problems with MDCT, assessment is sometimes difficult in patients who have trouble holding their breath, tachycardia or arrhythmias, or severely calcified lesions.[957]

**ii) Assessment of Coronary Artery Calcification**

Quantitative assessment of coronary artery calcification by electron-beam CT is useful for predicting coronary artery stenosis and cardiac events,[513,966] and MDCT shows the same accuracy as electron-beam CT.[2,489,967] The extent of calcified stenotic coronary artery lesions is related to coronary stenotic lesions and can be determined with high sensitivity; however, specificity is low.[967,968] The ACCF/AHA has stated that quantification of coronary arteriosclе-

rosis is useful in asymptomatic intermediate-risk patients for whom the 10-year incidence of cardiovascular events is estimated to be 10–20% based on the Framingham risk score, etc., but quantitation of coronary arteriosclerosis is not recommended for low-risk or high-risk patients.[969] There are racial differences in the onset and progression of coronary artery calcification. It has been reported that the incidence of coronary artery calcification is lower in Japanese than in American patients, even when their blood pressure and LDL-cholesterol levels are higher.[970] In a Japanese study of 374 patients, the sensitivity and specificity of MDCT for detecting calcified coronary artery stenosis was 75% and 92%, respectively.[971] However, that study included patients who underwent coronary angiography and cannot be used to assess the sensitivity and specificity of MDCT as a screening test.[967] Subanalysis of CORE64,[962] a multicenter study performed in 7 countries, including Japan, showed that among patients with suspected symptomatic coronary heart disease, ≈20% of those with no coronary artery calcification on 64-row MDCT had lesions causing ≥50% stenosis, which indicates that absence of coronary artery calcification does not preclude subsequent coronary angiography in symptomatic patients.[972]

#### iii) Assessment of Vulnerable Plaques

MDCT (64-row or more) can be used to assess plaque quality, which cannot be determined by coronary angiography. MDCT identifies vulnerable plaques based on microcalcification, positive remodeling, low CT values, and the napkin-ring sign, as well as showing the extent of stenosis.[973,974] The napkin-ring sign is a ring-shaped area of high attenuation surrounding a low-attenuation plaque and is an independent predictor of ACS, together with positive remodeling and a low CT value.[975]

### b. Cardiac MRI

Recent advances in technology have been followed by rapid accumulation of evidence that cardiac MRI is useful for both diagnosis and determining the treatment strategies for coronary heart disease.[2,618,976] In addition to accurate assessment of cardiac function and regional wall motion by cine MRI,[608] LGE MRI shows higher diagnostic sensitivity for subendocardial infarction than myocardial SPECT.[597] Compared with MDCT, however, the imaging time is longer and spatial resolution is insufficient. Moreover, assessment of the coronary stent lumen is difficult, and cardiac MRI cannot be performed in patients with pacemakers or ICDs that do not support MRI. Still, it is expected to become a useful noninvasive method for assessment of coronary artery lesions without radiation exposure. Recently, some conditionally MRI-compatible ICDs have become available, but safe performance of MRI requires support at accredited facilities,[977] and there is a high frequency of images being affected by metal artifacts from the device.

#### i) Coronary MRA

Coronary MRA has advantages over cardiac MDCT, including (1) no radiation exposure, (2) no need for contrast agents, and (3) no influence of severe coronary artery calcification on image quality.[2,976] Whole-heart coronary MRA uses respiratory and electrocardiographic gating to obtain 3-dimensional images of the entire heart.[615] The sensitivity and specificity of coronary MRA for coronary artery stenosis are reported to be 78% and 91–96%, respectively,[616,978] ad a Japanese multicenter study found a sensitivity of 88%, specificity of 72%, positive predictive value of 71%, and negative predictive value of 88%.[633] It was recently reported that high-intensity lesions on unenhanced T1-weighted images correspond to vulnerable plaques with a low CT value on MDCT,[979] that high-intensity plaques are associated with cardiac events,[980] and that stabilization of plaques by statin therapy can be detected on unenhanced T1-weighted images.[981] These findings have made qualitative assessment of coronary artery plaques by MRI possible.

Coronary MRA is useful for evaluating coronary artery anomalies in young people and coronary artery aneurysms in patients with Kawasaki disease where radiation exposure is a concern. It is also useful for assessment of the coronary arteries in patients with renal failure, because contrast agents are unnecessary. Furthermore, coronary MRA can be performed in patients with severe coronary artery calcification.[2,615,616] Accordingly, it is expected to play a role as a screening test instead of coronary angiography in the future. However, stented regions of vessels cannot be visualized, due to metal artifacts, and coronary MRA is therefore unsuitable for assessment of restenosis.[2]

#### ii) Stress Myocardial Perfusion MRI

Investigation of myocardial ischemia is important to assess the influence of morphological coronary artery stenosis and to improve the prognosis by performing PCI.[613] When stress myocardial perfusion MRI is performed, a gadolinium contrast agent is administered and the distribution of myocardial blood flow is assessed from the first-pass dynamics of the contrast agent under pharmacological stress such as adenosine. A meta-analysis showed that stress myocardial perfusion MRI had an average diagnostic sensitivity of 89% and specificity of 76% for coronary artery stenosis.[934] In comparison with myocardial SPECT, which is widely used for the diagnosis of myocardial ischemia, stress myocardial perfusion MRI showed excellent diagnostic performance for detection of coronary artery stenosis. In particular, it was significantly superior to myocardial SPECT in patients with multivessel disease.[597] In a meta-analysis using FFR as the gold standard for functional evaluation of coronary artery stenosis, stress myocardial perfusion MRI was superior to stress myocardial SPECT for detection of significant stenosis.[265]

During the preoperative coronary artery assessment of patients with aortic aneurysms, it is better to avoid coronary angiography because of its risks, but MDCT may not be sufficient for diagnosis, because of severe calcification, suggesting that cardiac MRI may be beneficial in such cases.[982] For assessment of coronary artery lesions by MRI, see the respective methods in this Guideline.

### c. Echocardiography

Echocardiography has advantages such as low cost, no radiation exposure, and able to be performed at the bedside. Its disadvantages include the need to train operators and poor image quality in patients with a certain body size. Typical methods used to diagnose coronary artery lesions are detection of myocardial wall motion abnormality caused by ischemia, and direct visualization of coronary artery stenosis from blood flow velocity signals.[2]

#### i) Stress Echocardiography

Unlike stress ECG, stress echocardiography can be performed in patients with ST-segment or T-wave changes on

the resting ECG caused by digoxin use, left bundle branch block, or left ventricular hypertrophy, and it has a high diagnostic accuracy.[983] Coronary artery stenosis is diagnosed by detecting left ventricular regional wall motion abnormalities due to myocardial ischemia induced by exercise (treadmill or ergometer) or by pharmacological stress (dobutamine or dipyridamole).[984] With exercise stress, a standard cross-sectional image is obtained before and immediately after stress loading, and the culprit coronary artery lesion is inferred from the wall motion abnormality in each segment of the left ventricular myocardium. Pharmacological stress can be used in patients who have difficulty performing exercise, and dobutamine challenge is generally performed.[984] Standard cross-sectional images are recorded before drug infusion, at a low drug dose, at a high drug dose, and after drug infusion in order to diagnose coronary artery stenosis from the changes in wall motion in each myocardial segment.

Investigation of the diagnostic performance of exercise echocardiography has shown a sensitivity of 86%, specificity of 81%, and diagnostic accuracy of 85%.[983,985] With regard to its performance for diagnosis of significant coronary artery stenosis using dobutamine stress, the sensitivity is 82%, specificity is 84%, and diagnostic accuracy is 83%.[983,986–989] The diagnostic rate for coronary artery lesions is similar to that of radionuclide imaging. Although the equipment is simpler and less expensive than for other methods,[2] interobserver variability is large and a highly skilled operator is required. Use of transvenous contrast to enhance the visibility of wall motion, application of 3-dimensional echocardiography to simplify image acquisition, and application of tissue Doppler and tissue tracking methods to objectively evaluate wall motion are expected in the future.[984]

#### ii) Evaluation of Coronary Flow Velocity

Advances in Doppler ultrasonography have enabled direct visualization of coronary flow velocity signals, allowing noninvasive diagnosis of coronary artery lesions based on evaluation of CFR and visualization of stenotic blood flow.[134] Coronary flow velocity signals are visualized by the color Doppler method, and coronary flow profile is recorded by the pulsed Doppler method.[2] The detection rate of blood flow in the left anterior descending artery is as high as 90%, but the detection rate of the right coronary artery and left circumflex artery is slightly lower.[984] In patients with coronary artery stenosis, the normal diastolic dominance of flow velocity is lost, and a characteristic waveform is noted, with slow blood flow persisting throughout the cardiac cycle. Measurement of CFR with ATP or dipyridamole stress loading has been found to be useful for the diagnosis of mild lesions causing ≈50% coronary artery stenosis. It is not only useful for detecting coronary artery lesions, but also for identifying myocardial microvascular obstruction.[134,990,991] For evaluation of coronary artery lesions by echocardiography, refer to the individual methods in this Guideline.

### d. Cardiac Radionuclide Imaging

Cardiac radionuclide imaging allows noninvasive, physiological imaging, and stress and rest myocardial perfusion SPECT are widely used for the diagnosis of coronary heart disease in daily clinical practice. If exercise stress loading is impossible or contraindicated, myocardial ischemia can still be diagnosed by using vasodilators.[2] Regarding the diagnostic accuracy of exercise myocardial perfusion SPECT for coronary artery stenosis (≥50%), a sensitivity of 96% and a specificity of 36–96% have been reported. With adenosine stress loading, the sensitivity and specificity were 75–96% and 38–100%, respectively.[207] In the past, diagnostic accuracy was studied by comparison with morphological stenosis on coronary angiography. However, the diagnostic accuracy of myocardial perfusion SPECT has more recently been compared with that of FFR (≤0.8), which is a method used for evaluation of functional coronary artery stenosis.[262]

Because myocardial perfusion SPECT shows the relative blood flow distribution, there used to be a potential problem of false-negative results in patients with balanced ischemia due to triple-vessel disease or left main trunk disease.[218,266] However, development of a semiconductor gamma camera dedicated to the heart has made quantitative evaluation of myocardial blood flow possible,[267,268] and good diagnostic accuracy has been achieved for triple-vessel disease and left main trunk lesions, with a sensitivity of 86%, specificity of 78%, and accuracy of 80%.[269]

Quantitative measurement of ischemic myocardium is possible using stress myocardial blood flow SPECT. Coronary revascularization improves the prognosis compared with pharmacotherapy and the incidence of cardiac events increases as the amount of ischemic myocardium increases in the case of ischemic myocardium accounting for more than 10% of the total left ventricular myocardium.[227,300] Therefore, when determining the indications for coronary revascularization, it is recommended to confirm whether ischemic myocardium accounts for 10% or more of the total left ventricular myocardium by performing stress myocardial perfusion SPECT, etc.[127] For assessment of coronary artery lesions by radionuclide imaging, see the sections on each test in this Guideline.

## 2.1.3 Invasive Evaluation

Although noninvasive modalities such as MDCT have become available for assessing coronary artery stenosis, coronary angiography remains the gold standard. Conventionally, in addition to the criterion that 75% should be the threshold for significant stenosis as in the AHA classification, quantitative measurements can be carried out, such as edge detection and video densitometry.[642] Quantitative assessment is essential to monitor changes over time in the same patient, such as assessing a lesion before and after PCI or the response to drug therapy in an interventional study.[992]

Findings obtained by IVUS have shown that coronary angiography alone cannot adequately assess the clinical significance of coronary artery stenosis.[993,994] Because coronary angiography provides a projection of the vessel lumen, the characteristics of the vessel wall and the extent of vascular remodeling cannot be assessed. If a lesion only causes moderate stenosis, the presence or absence of ischemia is a key point.[730] In such cases, functional evaluation using a pressure guidewire[568] or Doppler guidewire[764] is useful, in addition to morphological assessment by IVUS, angioscopy, etc. Obtaining the FFR at the time of coronary angiography to assess the functional severity of coronary artery stenosis can help to determine whether a lesion is causing myocardial ischemia and to make decisions about treatment strategies.[995] Care should be exercised in patients who have microvascular obstruction, such as those with myocardial hypertrophy or diabetes mellitus, as CFR will

decrease even in the absence of coronary artery stenosis.

## 2.2 Coronary Artery Lesion Assessment in Myocardial Infarction

### 2.2.1 Targets for Evaluation

When evaluating coronary artery stenosis in patients with myocardial infarction, the presence/absence of residual myocardium in the infarct zone, the presence/absence of ischemia in the noninfarct zone, and left heart function are also important factors to consider.[996,997] If angina symptoms are present, the extent of coronary artery stenosis should be examined in the infarcted and noninfarcted regions of the myocardium. Determining the presence/absence of objective ischemic findings is important in patients with myocardial infarction, because asymptomatic ischemia is common. In patients with poor left ventricular function (LVEF <40%), assessing the extent of coronary artery stenosis is essential to predict the prognosis.

### 2.2.2 Evaluating the Extent of Stenosis

Evaluation of coronary artery lesions in the noninfarcted areas is performed similarly to evaluation of lesions in patients with stable coronary heart disease. With regard to evaluation of ischemia in the infarct zone, microvascular obstruction in the myocardium modifies the CFR, raising the possibility that functional evaluation may not correctly assess the extent of stenosis. Therefore, assessment of coronary artery stenosis is performed by morphological assessment. MDCT is used for noninvasive testing.

In Japan, revascularization by PCI is frequently performed in patients with myocardial infarction, and MRA, which cannot examine the stent lumen, is not appropriate for evaluating the culprit coronary artery.[2] Invasive evaluation methods include coronary angiography, IVUS, angioscopy, and OCT. Particularly, IVUS and OCT have additional value for detecting plaque rupture at the culprit lesion, and angioscopy can diagnose unstable lesions by observing yellow plaques or thrombi.[950]

### 2.2.3 Postinfarction Angina and Asymptomatic Myocardial Ischemia

Postinfarction angina is angina that occurs following myocardial infarction. Its incidence is 20% in patients receiving thrombolytic therapy alone and 6% in those treated by PCI,[998,999] and the incidence is even lower with stenting.[1000] Postinfarction angina is classified according to the site of ischemia (noninfarcted or infarcted myocardium). If it does not respond to adequate medical therapy, coronary angiography is performed.[1001] Patients with asymptomatic myocardial ischemia do not have anginal pain or similar symptoms, but transient myocardial ischemia can be detected by ECG, radionuclide imaging, etc. Cohn reported that asymptomatic residual ischemia existed in 20–50% of patients after myocardial infarction.[1002] If ischemia is objectively documented, active treatment should be performed, even in asymptomatic patients.[955,956,1003] It has also been reported that vulnerable plaques are more common in patients with a history of myocardial infarction.[1004] These patients are referred to as "vulnerable patients" (patients with vulnerable plaques) and have a high risk of recurrence.[1005] An MDCT study showed that ACS is more likely to occur in patients with lesions that display positive remodeling associated with low-attenuation plaque.[541] Evaluation of both microvascular obstruction after myocardial infarction[1006] and myocardial viability, which can be assessed by cardiac MRI, has recently become possible by contrast-enhanced MDCT as well.[1007] In the future, noninvasive tests such as MDCT will become important in addition to use of intravascular imaging to identify "vulnerable patients," so that ACS can be prevented in patients with chronic coronary heart disease.

## 2.3 Assessment of Myocardial Ischemia and Lesions Associated With PCI

Assessment of myocardial ischemia and coronary artery lesions is essential to determine the indications for PCI. According to a new requirement in the 2018 revision of remuneration for medical care services, the presence of functional myocardial ischemia should be demonstrated by preoperative examinations, etc. when performing elective PCI or percutaneous coronary stenting for stable coronary heart disease. That is, a clear medical rationale is required to perform PCI and stenting. Specifically, unidirectional imaging of >75% stenosis is sufficient for ACS (acute myocardial infarction and unstable angina), but the following requirements need to be satisfied for stable coronary heart disease: (1) >90% stenosis, (2) a stenotic lesion that is thought to cause stable effort angina (only in the absence of other significant lesions), and (3) additional diagnostic testing for functional ischemia that identifies the stenotic lesion as the cause of functional ischemia. This suggests that the need for noninvasive tests such as CCTA, cardiac MRI, echocardiography, and radionuclide imaging is likely to increase in the future, as well as Doppler and pressure guidewire testing to assess functional myocardial ischemia. On the other hand, invasive assessment is essential for selecting the devices for PCI and deciding treatment endpoints.

### 2.3.1 Selection of Devices

Quantitative measurement of vessel diameter by coronary angiography or intracoronary imaging is essential to determine the size of the balloon or stent for PCI. Use of IVUS or OCT not only allows evaluation of the extent of luminal stenosis, but also observation of the vessel walls and plaque characteristics, such as calcification, that are not evident on coronary angiography,[1008–1010] providing important information for selection of PCI devices.[1011]

### 2.3.2 Deciding the Endpoints

A recent comparison of coronary angiography-guided and IVUS-guided PCI showed that better outcomes were obtained by angiography-guided PCI.[1012,1013] Predictors of stent thrombosis or restenosis after stenting include poor stent expansion, residual disease, thrombus, and coronary artery dissection. The minimum stent area is also a predictor of in-stent restenosis, and IVUS observation can provide useful information for determining PCI endpoints.[1014,1015]

### 2.3.3 Post-Treatment Evaluation and Follow-up

There is some risk of restenosis after PCI, however it is performed. The incidence of restenosis is 5–10% when DES are used, which is significantly lower than with conventional stents (bare metal stents),[1016–1021] but the problem of late stent thrombosis is a concern.[1022] In Japan, coronary angiography is sometimes performed ≈6 months after PCI to check for restenosis. However, the recent ReACT study performed in Japan found no clinical benefit of follow-up

coronary angiography at 8–12 months after PCI, and there was a higher incidence of target lesion revascularization within 1 year in the follow-up angiography group.[647]

Post-treatment assessment and follow-up using noninvasive techniques such as MDCT and cardiac MRI would be meaningful if it could be achieved. With MDCT, it is possible to identify changes in coronary artery lesions, including plaque progression and regression, and detect noncalcified vulnerable plaques, as well as the changes in treated lesions. Assessment of the stent lumen by MDCT has already been successful for stents of ≥3 mm placed at a proximal site. Coronary MRA cannot visualize the stent lumen, but the presence/absence of myocardial ischemia on stress myocardial perfusion MRI may allow the diagnosis of restenosis.[2]

**Table 51. Recommendations and Levels of Evidence for Testing Methods to Assess Coronary Artery Lesions**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **Coronary angiography** | | | | |
| Anatomical assessment | I | C | B | V |
| Assessment of stenotic lesions | I | B | A | III |
| Assessment of vulnerable plaque | IIb | C | C1 | IVb |
| **CCTA** | | | | |
| Anatomical assessment | I | B | B | IVb |
| Assessment of stenotic lesions | IIa | B | B | II |
| Assessment of vulnerable plaque | IIa | B | B | II |
| **Cardiac MRI** | | | | |
| Anatomical assessment | I | C | B | V |
| Assessment of stenotic lesions | IIa | B | B | II |
| Assessment of vulnerable plaque | IIb | C | C1 | IVb |
| **Echocardiography** | | | | |
| Assessment of stenotic lesions | IIb | C | C1 | IVb |
| **Cardiac radionuclide imaging** | | | | |
| Assessment of stenotic lesions | IIa | B | C1 | II |
| **IVUS/OCT** | | | | |
| Assessment of stenotic lesions | IIa | B | B | III |
| Assessment of vulnerable plaque | IIa | B | B | III |
| **Angioscopy** | | | | |
| Assessment of stenotic lesions | IIb | B | C1 | III |
| Assessment of vulnerable plaque | IIb | B | C1 | III |
| **Coronary blood flow measurement** | | | | |
| Assessment of stenotic lesions | IIb | C | B | IVb |
| **Intracoronary pressure measurement** | | | | |
| Assessment of stenotic lesions | I | A | A | I |

CCTA, coronary computed tomography angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

## 3. Diagnosis of Myocardial Viability

Myocardial viability indicates myocardial characteristics by which contractility is preserved or impaired by myocardial infarction or severe ischemia. However, contrctility may be improved by appropriate revascularization therapy for the ischemic region.[1023] This concept was derived from the observation that revascularization for coronary heart disease, mainly by PCI and CABG procedures, often improves the function of myocardial regions with reduced contractility and that regions responding to positive inotropic stimulation responded to revascularization. Thus, the concept of myocardial viability is clinically oriented, but requires assessment of blood flow and metabolism, as well as global and regional left ventricular function. If viable myocardium is present near the endocardium, myocardial contractility may be restored by alleviating ischemia, even in patients with myocardial infarction. Therefore, accurate diagnosis of viable myocardium is essential when determining the indications for PCI and CABG. When myocardial perfusion SPECT imaging and dobutamine stress transthoracic echocardiography (TTE) are performed, greater recovery of left ventricular function is associated with a more favorable prognosis,[229,1024] and thus is highly useful for predicting the patient's prognosis.

Myocardial viability covers 2 conditions: hibernating and stunned myocardium. Hibernating myocardium is viable myocardium that is affected by severe ischemia from severe coronary stenosis and has lost its contractility.[154] Hibernating myocardium may persist for several months, similar to an animal that is hibernating and waiting for spring. In this condition, myocardial contractility can be improved by revascularization of the ischemic region or by reducing myocardial oxygen demand.[1023] It is thought that regional metabolism decreases to prevent myocardial necrosis by reducing energy consumption, and revascularization is an effective treatment for myocardium in this state.

Stunned myocardium is myocardium that has been exposed to severe ischemia and shows persistent loss of left ventricular contractility even after ischemia resolves.[1025] Stunned myocardium was first discovered in an animal study when the recovery of left ventricular wall motion was delayed after resolution of transient ischemia caused by coronary ligation. Clinically, stunned myocardium is observed after revascularization is performed for effort angina, vasospastic angina, or myocardial infarction. Stunned myocardium can be likened to animals that remain stunned for a certain period after a crisis. Impairment of cardiac contraction due to stunned myocardium usually resolves within a few hours. However, in chronic myocardial stunning, the stunned myocardium may persist for weeks after revascularization for myocardial infarction. Because blood flow has already been restored to the sites of stunned myocardium, diagnosis requires confirmation of the presence of blood flow by coronary angiography or radionuclide imaging.

Recently, it was reported that resting blood flow and oxygen metabolism are relatively maintained in some areas

of hibernating myocardium; therefore, some cases cannot be explained by the theory outlined above. Another hypothesis of hibernating myocardium is that repeated intermittent myocardial stunning causes hibernation, because the perfusion reserve is reduced in hibernating myocardium.[1025–1027] It is also unclear whether stunned and hibernating myocardium are sequential or occur independently of each other. Pathologically, the sarcolemma is decreased in hibernating myocardium, but the cell volume of the cardiomyocytes is not decreased. Restoration of contractility is associated with de-differentiation, but if there are advanced pathological changes, the extent of recovery and prognosis are poor. Whether it is hibernating myocardium or stunned myocardium, detection of viable myocardium is very important both scientifically and clinically. However, currently, there is no generally accepted definition of myocardial viability. In addition, it is important to noninvasively assess the 3-dimensional anatomy of the LV with good spatial and temporal resolution, as well as accurate evaluation of blood flow, metabolism, cardiomyocyte membrane function, and left ventricular systolic and diastolic function.Recommendations and levels of evidence for assessing coronary lesions are shown in **Table 51**.

## 3.1 Detection Using Various Diagnostic Modalities

### 3.1.1 ECG

Assessment of myocardial viability by ECG is based on the presence of abnormal Q waves, ST elevation, exercise ECG findings, and QT dispersion. The presence of abnormal Q waves reflects transmural necrosis of the myocardium just below the lead site, and the extent of necrotic myocardium can be estimated from the number of leads with abnormal Q waves. However, there can be some viable areas in the estimated infarcted myocardium of patients with Q-wave myocardial infarction.

In patients with myocardial infarction, ST elevation occurs frequently in leads over the infarct zone during exercise. This underlying mechanism may include ischemia of the residual viable myocardium in the infarct zone or reciprocal changes in the contralateral myocardium. However, exercise-induced deterioration of left ventricular wall motion may also cause such a phenomenon; therefore, the occurrence of ST elevation does not always suggest the presence of ischemia or indicate myocardial viability. A study evaluating the mechanism of exercise-induced ST elevation by comparison with F-18 FDG PET[35] revealed that ST elevation showed a sensitivity of 66% and a specificity of 100% for the diagnosis of myocardial viability, and ST elevation in the infarct zone during dobutamine challenge had a sensitivity of 69% and a specificity of 83% for the diagnosis of myocardial viability.[1028] Thus, specificity was good in both cases, but sensitivity was not excellent. In patients with single-vessel disease and myocardial infarction, ST depression in the noninfarct zone during exercise corresponded to myocardial viability on F-18 FDG-PET with a sensitivity of 84% and a specificity of 100%.[1029] However, it is problematic to use ST depression as an indicator of myocardial viability in the infarct zone in patients with multivessel disease. Positive conversion of negative T waves and negative conversion of positive U waves have also been studied.[1029,1030]

QT dispersion, which is the difference between the maximum and minimum QT intervals among the leads on the standard 12-lead ECG, has attracted attention as a prognostic factor in patients with conditions such as heart failure and myocardial infarction. This index is known to increase in patients with acute myocardial ischemia and can be used as a marker of myocardial ischemia. In a study on detection of myocardial viability by QT dispersion compared with F-18 FDG-PET performed in 44 patients with previous myocardial infarction,[1031] a QT dispersion ≥70 ms showed a sensitivity and specificity for myocardial viability of 83% and 71%, respectively.

As described above, assessment of myocardial viability by ECG has several limitations, and it should only be used as necessary in the case of other tests not being able to be performed.

### 3.1.2 Transthoracic Echocardiography (TTE)

Resting TTE is widely used for the diagnosis and evaluation of chronic coronary heart disease because it is noninvasive, convenient, and has rapid image acquisition. However, its diagnostic performance depends highly on the quality of the images obtained. Moreover, resting TTE only provides semiquantitative evaluation and the quality of the images obtained and the results are influenced by the skill and experience of the operator. The detection of myocardial viability using TTE is based mainly on the contractile reserve in loading tests, and assessment has been carried out using contrast medium in recent years.

#### a. Evaluation of LV Morphology

In patients with previous myocardial infarction, the presence of mural thinning, increased echogenicity in the left ventricular (LV) myocardium, and LV aneurysm formation are indicators of the presence of severe LV myocardial fibrosis, and myocardial viability can be poor at sites showing such changes. If the LV wall does not show thinning in the chronic phase of infarction, there may be a possibility of hibernating or stunned myocardium, even in the absence of LV wall motion.

#### b. Evaluation of LV Wall Motion and Dobutamine Stress Test

Tracing the movement of the LV endocardium is used as the basis for evaluating LV wall motion by TTE, with contour extraction being carried out manually or automatically using B-mode images. LV wall motion is assessed by the centerline method to avoid the effects of anteroposterior cardiac movement. Both the movement of the endocardium and the increment in LV wall thickness during systole are evaluated.

The presence of LV wall movement in the resting state is evidence of myocardial viability, but it is difficult to distinguish between hibernating or stunned myocardium by resting TTE alone if the LV wall motion is severely impaired. Therefore, a pharmacological stress test should be performed to see whether wall motion is altered. Among the various tests, dobutamine loading is the most popular. A coronary artery occlusion/reperfusion study showed that intravenous infusion of dobutamine at a rate of 10 $\mu$g/kg/min restores LV wall motion in areas of akinesis or hypokinesis.[1032] Regarding the diagnosis of myocardial viability by stress TTE, several observational studies have shown that patients with detectable myocardial viability may have an improved prognosis after revascularization.[1033,1034] Impaired LV wall motion after thrombolytic therapy for acute myocardial infarction, which indicates myocardial stunning, is improved by dobutamine administration.[1035]

| Table 52. Contraindications for Dobutamine Stress Echocardiography |
|---|
| Acute myocardial infarction (within 4–10 days after onset) |
| Unstable angina |
| Patients with documented left main trunk artery stenosis |
| Obvious congestive heart failure |
| Severe, life-threatening tachyarrhythmia |
| Severe valvular stenosis |
| Hypertrophic obstructive cardiomyopathy |
| Acute pericarditis/myocarditis and endocarditis |
| Aortic dissection |

(Reproduced from Krahwinkl et al 1997,[1043] with permission from Oxford University Press on behalf of the European Society of Cardiology. OUP and the ESC are not responsible or in any way liable for the accuracy of the translation. The Japanese Circulation Society is solely responsible for the translation in this publication/reprint.)

It has also been shown that restoration of LV wall motion after revascularization can be predicted by improvement of impaired LV wall motion, an indication of hibernating myocardium, during dobutamine stress TTE in patients with multivessel disease.[1036] Charney et al compared dobutamine stress TTE with resting thallium-201 (Tl-201) cardiac perfusion SPECT and showed that the ability to predict myocardial viability after revascularization was similar but TTE was less expensive than resting Tl-201 SPECT.[1037] When low-dose dobutamine stress TTE is performed to assess myocardial viability, the infusion of dobutamine is usually started at 2 $\mu$g/kg/min and blood pressure is measured every minute together with monitoring of the ECG. If there are no symptoms, ST changes on the ECG, frequent occurrence of arrhythmias, marked elevation of blood pressure (≥200 mmHg), or a decrease in systolic blood pressure by ≥20 mmHg, the infusion rate is increased by 2 $\mu$g/kg/min every 3 min up to 10 $\mu$g/kg/min.

The LV long-axis, short-axis, apical 2-chamber, and 4-chamber images are recorded before dobutamine loading and during each loading stage, and then the TTE images obtained before and after loading are displayed simultaneously for visual judgment of LV wall motion. Viable myocardium can be present when LV wall motion is improved in akinetic or severely hypokinetic regions. The sensitivity and specificity of low-dose dobutamine stress TTE for detecting viable myocardium is reported to be 80–90%.[143,1036,1038–1042] The most common adverse reaction to dobutamine is induction of arrhythmia, generally premature supraventricular or ventricular contractions. If supraventricular or ventricular tachycardia occurs, testing should be discontinued. If anginal pain occurs, the test should also be discontinued and nitroglycerin should be given immediately either sublingually or as a spray. As with other stress tests, emergency drugs and a cardiac defibrillator should be available. Contraindications to dobutamine stress testing are similar to those for other stress tests and generally include (1) acute myocardial infarction (4–10 days previously), (2) unstable angina, (3) known left main trunk artery stenosis, (4) obvious congestive heart failure, (5) severe, life-threatening tachyarrhythmia, (6) severe valvular stenosis, (7) hypertrophic obstructive cardiomyopathy, (8) acute pericarditis/myocarditis and endocarditis, and (9) aortic dissection (**Table 52**).[1043] Direct observation is the usual method of detecting abnormal LV wall motion.

However, for detecting viable myocardium, strain imaging, which is a new method for accurate assessment of regional myocardial motion, has been reported in recent years,[1044,1045] and concomitant use of strain imaging with direct LV wall motion observation may improve sensitivity. The disadvantages of using stress TTE for the evaluation of myocardial viability include poor delineation, qualitative judgment, and low inter-rater reproducibility. However, it was reported that use of the tissue Doppler method[1046] to detect myocardial contraction in combination with dobutamine stress TTE improved the accuracy of assessing myocardial viability and exercise tolerance.[1047] Other stress loading modalities include exercise, dipyridamole,[1033] adenosine triphosphate, and nitroglycerin, but their usefulness is less clear compared with dobutamine stress.

### c. Myocardial Contrast TTE

When selective coronary arteriography is performed, myocardial contrast TTE is being used more frequently to evaluate peripheral run-off after intracoronary injection of a contrast agent for judgment of myocardial viability. Theoretically, myocardial contrast TTE is useful for the evaluation of myocardial stunning in patients with acute myocardial infarction undergoing revascularization. Unlike the determination of contractile reserve by dobutamine stress TTE, myocardial contrast TTE is not affected by factors such as residual coronary artery stenosis, coronary reserve, myocardial necrosis, or interstitial fibrosis. According to a cohort study, myocardial contrast TTE showed lower specificity compared with Tl scintigraphy for detecting viable myocardium related to restoration of cardiac function, but its sensitivity was comparable.[1048] The combination of myocardial contrast TTE and dobutamine stress TTE is expected to improve sensitivity in the future. However, the use of current contrast agents for the heart is not covered by health insurance at present.

Even when revascularization is successful, poor inflow of contrast medium into the infarcted myocardium may occur;[198,1049] that is, the "no-reflow" phenomenon, which is considered to indicate microvascular obstruction due to reperfusion injury. Myocardium exhibiting the no-reflow phenomenon shows delayed recovery of wall motion after revascularization, and abnormal LV wall motion often persists. Various intravenous contrast media have been developed recently, leading to the possibility of evaluating myocardial viability by injecting contrast medium into a peripheral vein. Although previous transvenous myocardial contrast TTE techniques only achieved poor image quality, the development of echo contrast agents and advances in ultrasound devices have improved image quality. Wide clinical application has been promoted by use of various noise reduction methods based on second harmonic imaging and intermittent transmission to minimize the destruction of microbubbles by ultrasonic waves. There is no contrast staining of nonviable tissues where the culprit coronary artery is completely occluded and the myocardium is largely fibrotic.

## 3.1.3 Cardiac Radionuclide Imaging

With regard to assessment of myocardial viability by radionuclide imaging, Tl-201, technetium-99 m (Tc-99 m), I-123-BMIPP, and I-123-meta-iodobenzyl-guanidine (MIBG) are used for SPECT, with $^{18}$F-FDG and nitrogen-13 ammonia being used for PET in the clinical setting. PET

tracers, such as oxygen-15-labeled water and rubidium-82, are not yet covered by health insurance, but are expected to be used in the future.

### a. Tl-201

Myocardial perfusion imaging is the main cardiac radionuclide imaging modality and is used to diagnose and assess coronary heart disease. Tl-201 is an analog of potassium that is actively taken up by cardiomyocytes via Na/K ATPase, allowing assessment of myocardial viability based on membrane integrity. After being injected intravenously, Tl-201 is distributed in proportion to myocardial blood flow and is taken up by cardiomyocytes. Regions of ischemia and infarcts are depicted as reduced Tl-201 accumulation. Tl-201 redistribution occurs because when blood flow is decreased in ischemic myocardium, washout is slower than in normal myocardium or infarcted myocardium and the region of reduced accumulation in the early image appeared to improve the accumulation in the delayed image (obtained after 3–4 hours).[1050]

The differentiation of ischemic myocardium and infarcted myocardium is based routinely on the presence of redistribution. However, 30–50% of the myocardial areas without redistribution of Tl-201 still show restoration of cardiac function after revascularization, and poor sensitivity is a problem when predicting recovery of LV systolic function based on redistribution.[1051] To improve sensitivity, redistribution is assessed at 24 hours or in the resting state,[1052] or an additional dose of Tl-201 is administered (reinjection method)[1053] after late exercise imaging. According to a review by Bax et al, although Tl-201 shows good sensitivity for the assessment of viability, it has lower specificity compared with TTE.[232] Attempts have been made to improve accuracy by adding information on cardiac function and by correction of SPECT attenuation. Innovations in imaging equipment have enabled fusion images with CT to be obtained,[1054] and application to correction of attenuation is expected in the future.

### b. Tc-99m-Labeled Myocardial Perfusion Agents

Using Tc-99m-labeled myocardial perfusion agents such as Tc-99m MIBI and Tc-99m tetrofosmin, myocardial viability can be assessed from accumulation, as with Tl-201. These agents have been reported to achieve detectability comparable to that of Tl-201.[1055,1056] In most studies, viable myocardium was defined as areas where Tc-99m-labeled myocardial perfusion agents showed at least 50–60% accumulation relative to normal myocardium, and this definition is widely accepted.[234,305,1055]

With Tc-99m-labeled myocardial perfusion agents, indices of LV function can be calculated easily by the first-pass technique or by ECG-gated myocardial perfusion SPECT. Therefore, the accuracy of assessing myocardial viability can be improved by considering information such as LV wall motion and changes in wall thickness in addition to myocardial blood flow.[1057,1058] These methods are useful for predicting cardiac function after revascularization.[1059,1060] A Japanese prospective multicenter observational study of resting ECG-gated Tc-99m-MIBI SPECT also showed good reproducibility of both functional information and myocardial accumulation, and combining such information was found to be useful for predicting the improvement of LV wall motion after revascularization.[304] Dobutamine stress ECG-gated myocardial perfusion SPECT is also useful for the diagnosis of myocardial viability based on cardiac functional reserve.[1061–1063]

Because retention of Tc-99m MIBI is associated with decreased mitochondrial function,[1064] attention has been paid to the relationships among Tc-99m MIBI washout and cardiac function, myocardial viability, and the prognosis in patients with heart failure and triple-vessel disease. A clinical investigation has already been reported,[1065] and future application is expected.

Tsai et al[1066] performed a meta-analysis of 8 studies comparing Tc-99m MIBI and Tc-99m tetrofosmin SPECT with PET as the gold standard for assessment of myocardial viability in patients with coronary heart disease. Under these conditions, they demonstrated an integrated sensitivity and specificity of 82% (95% CI: 81–84) and 88% (95% CI: 86–90), respectively, indicating that SPECT shows good detectability.

### c. Assessment of Metabolism Using PET

The main energy sources for the myocardium are free fatty acids and glucose. In the fasting state, healthy myocardium obtains more than 60% of its energy from fatty acids, whereas ischemic myocardium depends on utilizing glucose by glycolysis. As ischemia progresses, anaerobic glycolysis becomes predominant, and further progression leads to myocardial necrosis with loss of metabolism. Hence, it is possible to examine the presence and extent of myocardial ischemia in detail by measuring the local utilization of energy substrates in the myocardium. Blood flow data and the accumulation of $^{18}$F-FDG, which indicates glucose metabolism, can be obtained by PET. Regions of enhanced glucose metabolism associated with reduced myocardial function and blood flow represent hibernating myocardium,[406,452,1067] and regions where glucose metabolism is low with poor function and blood flow represent infarcted myocardium. This method can predict, with 80–90% accuracy, which areas of myocardium showing impaired function will recover after revascularization.[302]

Furthermore, a meta-analysis showed that patients with myocardial regions showing increased glucose metabolism associated with reduced function and blood flow are more likely to develop cardiac events, and thus require revascularization.[354] FDG-PET has a sensitivity of 88% and specificity of 73% according to a report on the prediction of restoration of cardiac function, indicating superior specificity over the evaluation of blood flow.[1055] Thus, FDG-PET has long been the gold standard for detecting viable and salvageable myocardium.[1068] A comparison with other diagnostic modalities by Bax et al showed that FDG-PET is the most sensitive modality for predicting recovery of LV wall motion, but dobutamine stress TTE had the highest specificity.[232] According to a meta-analysis of 9 studies (target LVEF <40%) that combined clinical data, FDG-PET had a sensitivity of 91% (80–100%) and a specificity of 61% (44–92%) for predicting functional recovery in regions of LV scar tissue and hibernating myocardium detected by PET.[232] Thus, the sensitivity of FDG-PET is higher than that of other diagnostic modalities, and it is the best option for assessment of myocardial viability, especially in patients with LV dysfunction for whom revascularization is being considered.

On the other hand, a meta-analysis of studies in which revascularization was performed based on the assessment of viability by FDG-PET showed that revascularization significantly improved the prognosis, but there was no difference between FDG-PET and stress TTE or SPECT.[354]

However, it is often impossible to obtain adequate images by other methods in patients with severe coronary heart disease, whereas PET can provide clear images and has an important role in such cases. The use of dobutamine challenge with FDG-PET has also been attempted.[1069]

FDG-PET has been covered by Japanese health insurance since 2002, and a domestic system for the supply of $^{18}$F-FDG is being established, making it possible to image glucose metabolism by installing a PET camera without a cyclotron. In addition, imaging of glucose metabolism is possible by attaching a special collimator or coincidence circuit to SPECT equipment. Although high-quality images like those provided by PET cannot be obtained with FDG SPECT, the evaluation of myocardial viability is comparable to that with PET.[1070]

#### d. Assessment of Myocardial Fatty Acid Metabolism Using SPECT

The introduction of I-123 BMIPP enabled the assessment of myocardial fatty acid metabolism by SPECT. After administration, I-123 BMIPP is taken up from the blood by the myocardium in the same way as free fatty acids and forms BMIPPCoA, which is partially transported to the mitochondria. Because of its side chains, BMIPP does not undergo $\beta$-oxidation and persists in the myocardium for a long time as a stored fatty acid. Thus, it is impossible to directly analyze the $\beta$-oxidation of fatty acids from myocardial washout, as can be done with linear fatty acids such as C-11-labeled palmitic acid. Instead, fatty acid utilization is analyzed from myocardial accumulation of I-123 BMIPP after administration.

In ischemic myocardium, dissociation is often noted, which means that the distribution of I-123 BMIPP is lower compared with the blood flow shown by Tl-201. This is thought to be due to reverse diffusion of I-123 BMIPP (which diffuses into cardiac myocytes in proportion to the blood flow) into the blood without being utilized, and may parallel the impaired utilization of fatty acids.[1071,1072] As increased $^{18}$F-FDG accumulation has been confirmed in myocardial regions showing such dissociation, this probably represents ischemic myocardium where energy metabolism has shifted from utilization of fatty acids to glucose.[1073] Capitalizing on this phenomenon, assessment of myocardial viability by combining data on blood flow and I-123 BMIPP accumulation becomes possible. When myocardial fatty acid metabolism was analyzed using BMIPP before and after revascularization,[415,1073,1074] functional recovery in the chronic phase was observed in myocardial regions where blood flow and metabolism showed dissociation. In contrast, regions where both blood flow and metabolism are reduced are considered to represent infarcted myocardium.

#### e. Future Challenges

Radionuclide imaging can provide useful information for assessing myocardial viability by analysis of the dynamics of tracer uptake by viable cardiomyocytes and cardiomyocyte energy metabolism. Previous assessments of myocardial viability focused on predicting functional recovery, but it is necessary to base the judgment on a broader perspective, such as improving QOL and prognosis. A semiconductor SPECT system for the heart, equipped with a cadmium–zinc–telluride detector, is now available.[1075] Semiconductor detectors enable efficient and accurate signal processing by directly converting gamma rays into electrical signals. Therefore, low-noise images with high resolution and reduced scattered radiation can be obtained. Combining a high-resolution reconstruction algorithm with a semiconductor detector provides excellent sensitivity, resolution, and imaging time. Reducing the doses of radiopharmaceuticals is also possible and high-energy resolution reduces the imaging time (patient burden), and the accuracy of simultaneous dual-nuclide acquisition is improved because energy peaks can easily be discriminated.

### 3.1.4 Cardiac MRI

#### a. Methods

Detection of myocardial viability by cardiac MRI can be divided into 2 categories: evaluation of cardiac morphology and wall motion with cine MRI, and diagnosis of fibrotic infarcts by LGE MRI.

##### i) Contractile Reserve

Two cardiac MRI findings are used to detect hibernating myocardium in the absence of contraction in the resting state: the retention of absolute wall thickness and the restoration of wall motion after stress loading. The former is defined as an end-diastolic wall thickness ≥5.5 mm, and the latter is usually defined as an increment in systolic wall thickness by ≥1 mm compared with end-diastolic thickness during low-dose dobutamine loading.[1076,1077] Either ECG-gated cine MRI or high-speed MRI can be used in this context. Dobutamine is administered by intravenous infusion at a rate of 10 $\mu$g/kg/min via a peripheral vein, and imaging is performed after 3–5 min. The tagging method may be used to evaluate LV wall motion during dobutamine challenge.[1078,1079] The sensitivity and specificity of the cardiac MRI contractile reserve for detecting viable myocardium is 88% and 87%, respectively, compared with assessment of viability by PET[1080] at 89% and 94%, respectively, on the basis of improvement of cardiac function.[1081]

Assessment of stunned myocardium is performed by a similar method. Low-dose dobutamine challenge has been reported to increase systolic wall thickness by ≥2 mm at sites of stunned myocardium,[1076] and quantitative assessment of regional cardiac function by tagging has also been attempted.[1080] According to a joint statement on dobutamine stress cardiac MRI from various Canadian academic societies (CCS/CAR/CANM/CNCS/CanSCMR Joint Position Statement on Advanced Noninvasive Cardiac Imaging),[1082] a meta-analysis of 10 studies with a total of 401 cases showed that the sensitivity and specificity of dobutamine stress cardiac MRI were 94% and 94%, respectively, for detection of myocardium with restoration of contractility during follow-up after revascularization, a result that was equal or better than dobutamine stress TTE.

##### ii) Detection of Myocardial Fibrosis by LGE on T1-Weighted MRI

LGE on T1-weighted MR images obtained with gadolinium contrast medium is the gold standard for the detection of myocardial fibrosis and is used to assess myocardial viability. Compared with SPECT or PET, cardiac MRI has superior spatial resolution, and the assessment of LGE allows for clarification of the location and function of myocardial regions with scarring/fibrosis, as well as the extent of lesions, such as whether they are transmural or subendocardial. Thus, unrecoverable myocardium with scarring/fibrosis can be identified with high diagnostic accuracy.[1083] Although a very high diagnostic concordance rate with radionuclide imaging of myocardial viability has been

shown for transmural infarction, 47% of the affected regions could not be detected by radionuclide modalities such as SPECT at sites of subendocardial infarction where <50% of the wall thickness showed contrast enhancement on cardiac MRI.[1084] As described above, LGE MRI can clearly show areas of myocardial fibrosis among regions of hibernating or stunned myocardium, and it is very useful for assessing the disease state and for determining the appropriate treatment strategy such as revascularization.

#### b. Features and Advantages

An important advantage to using MRI for the detection of myocardial viability is that there is no radiation exposure, unlike radionuclide imaging or CT. Because of its excellent spatial resolution, cardiac MRI can easily distinguish the boundary between the endocardial and epicardial surfaces. It is also possible to obtain the desired cross-sectional images for each cardiac phase. Disadvantages of cardiac MRI include a longer acquisition time and the need for a technician who is skilled at imaging and knowledgeable about pathological conditions. Artifacts caused by the heart beating and by breathing are a problem, but can be improved by high-speed imaging,[1085] ECG gating, and respiration gating. With the use of contrast medium, changes in intramyocardial contrast enhancement over time can be measured quantitatively. It is safe to say that the assessment of myocardial viability with LGE MRI is established clinically.

#### c. Diagnostic Performance

Assessing myocardial viability using FDG-PET in patients with chronic myocardial infarction is the gold standard, but the sensitivity and specificity of cardiac MRI for the detection of hibernating myocardium is 72% and 89%, respectively, based on the assessment of LV wall thickness. Low-dose dobutamine stress cardiac MRI provides more detailed information on stunned and hibernating myocardium,[1086] and may be used to predict the recovery of LV function and future cardiac events.[145,1076,1087,1088] In particular, accuracy for estimating the likelihood of recovery can potentially be improved when assessing the viability of myocardial regions that show LGE of 25–50% of the wall thickness.[1087] When transesophageal echocardiography and MRI were compared for examination of myocardial viability based on wall motion under dobutamine stress, transesophageal echocardiography showed a sensitivity of 77% and a specificity of 94%, while cardiac MRI had a sensitivity of 94% and a specificity of 100%.[1077] With regard to the diagnosis of myocardial stunning in patients undergoing revascularization after acute myocardial infarction using cardiac MRI for assessment of wall thickness, it was reported that the sensitivity was 92% and the specificity was 56% for predicting recovery of wall motion after 4–6 months, and the sensitivity and specificity improved to 89% and 94%, respectively, when the appearance of abnormal wall motion under dobutamine stress was used as the benchmark.[1081]

According to a joint statement on dobutamine stress cardiac MRI from various Canadian academic societies (CCS/CAR/CANM/CNCS/CanSCMR Joint Position Statement on Advanced Noninvasive Cardiac Imaging),[1082] a meta-analysis of 13 studies with a total of 357 patients showed that LGE had a sensitivity of 81% and a specificity of 83% for predicting recovery of LV function, a result comparable to that for PET and superior to SPECT.[623,1089,1090]

#### d. Indications and Contraindications

Cardiac MRI is indicated for many patients with coronary heart disease who have myocardium of unknown viability, especially when imaging of the LV wall motion is poor by TTE. Sharples et al[1088] recommend the following algorithm for the assessment of myocardial viability: (1) if the initial 2-dimensional TTE provides inadequate images of all or part of the LV, MRI should be performed, with an additional low-dose dobutamine stress cardiac MRI (if necessary); and (2) if 2D TTE provides adequate images of the entire LV, dobutamine stress TTE is recommended without cardiac MRI. However, there is no evidence from randomized controlled trials to support this algorithm or its cost-effectiveness.

The contraindications of MRI include internal metal implants and claustrophobia. However, some of the newer pacemakers, cardiac resynchronization therapy pacemakers, ICDs, and ICDs with biventricular pacing (cardiac resynchronization therapy defibrillator) are conditionally compatible with cardiac MRI. Use of gadolinium contrast medium in patients with severe renal dysfunction is limited by the risk of nephrogenic systemic fibrosis. In principle, use of gadolinium contrast medium should be avoided in patients with endstage renal disease on long-term dialysis and nondialysis patients with acute renal failure or chronic renal failure and an eGFR <30 mL/min/1.73 $m^2$ (calculated from the serum creatinine level). In MRI laboratories, it may not be easy to perform monitoring and emergency procedures; therefore, it is not appropriate to use this imaging modality in patients with advanced heart failure or those in whom severe arrhythmia may be provoked by dobutamine stress.

#### e. New Technologies

Recently, in the cardiac MRI field, quantitative measurement of myocardial extracellular volume by T1 mapping has become an important topic. In cases of diffuse myocardial fibrosis, LGE MRI may have difficulty in differentiating myocardium with diffuse myocardial fibrosis from normal myocardium. Moreover, because LGE MRI is a qualitative method, it cannot be used to assess slight changes in myocardial properties. The T1 mapping method has recently been developed for assessing myocardial tissue properties based on cardiac MRI, and it has become available in the clinical setting.[1091] This modality allows quantitative assessment of myocardial fibrosis as extracellular volume in patients with "diseases that cause diffuse myocardial fibrosis", such as hypertensive heart disease, aortic valve stenosis, etc.,[1092] and it is also actively used to assess myocardial viability in patients with myocardial infarction.[1093]

### 3.1.5 CT

The trend towards the use of multi-array cardiac CT peaked with the development of 320-row CT, after which new types of CT scanners were developed, such as dual-source CT, dual-energy CT, photon-counting CT, and spectrum CT.[1094,1095] Retrospective ECG gating allows measurement of LV wall thickness and assessment of LV wall motion, and new modalities for the assessment of the myocardium are emerging based on these technologies. In addition, myocardial fibrosis can be visualized with conventional MDCT, as with cardiac MRI, by using the appropriate

tube voltage and high tube current after injecting approximately 100 mL of iodinated contrast medium, and then creating images by iterative reconstruction.[1096]

### a. Methods and Diagnostic Performance

Although use of contrast medium is essential with CT, LV wall thickness can be measured and LV wall motion can be assessed by retrospective ECG-gated imaging. The spatial resolution is much better than with radionuclide imaging and MRI. When 4-dimensional LV wall motion analysis is performed, wall motion display is smoother with 20-frame imaging at 5% intervals of the cardiac cycle (20 equal parts) than with 10-frame imaging reconstruction from 10 images obtained by dividing 1 cardiac cycle (RR interval) into 10 equal parts.

However, the underlying temporal resolution remains the same for both methods, and is actually inferior to the temporal resolution of TTE or cardiac MRI. Despite this, a recent meta-analysis showed a strong correlation of LVEF, end-systolic volume, end-diastolic volume, and cardiac mass measured by CT with cardiac MRI as a benchmark (correlation coefficients of 0.93, 0.95, 0.93, and 0.96, respectively).[1097] Stress myocardial CT with pharmacological stress, for example, is a new imaging method that can obtain both anatomical information and physiological information such as data on myocardial perfusion.[1098]

### b. Advantages

Advantages of assessing myocardial viability by CT include: (1) ability to observe all areas of the heart compared with TTE, which has difficulty in observing the apex; (2) short acquisition time; (3) performed imaging in the acute phase without restriction because of internal metallic implants, unlike cardiac MRI; and (4) simultaneous evaluation of coronary artery stenosis and LV wall motion in a single examination. In patients with myocardial infarction, not only fibrosis, but also fatty degeneration[522] and calcification may occur in the infarcted myocardium. These changes can be detected from differences in CT attenuation on CT scans.

### c. Disadvantages

The disadvantages of CT include the need to use iodinated contrast medium and exposure to radiation. Delayed-enhancement imaging is more difficult with CT than with cardiac MRI because CT provides inferior image quality due to its lower contrast resolution.

### d. New Technologies

In general, imaging with a low tube voltage is desirable for CT to clearly delineate late enhancement, which suggests the presence of myocardial fibrosis. However, the radiation dose is often not sufficient even when the tube current is maximized, resulting in noisy images. The difference between first-generation and second-generation 320-row CT scanners is that the maximum tube current can be set higher for low-voltage imaging with the latter scanners, and a high-quality image with reduced noise can be obtained by iterative image reconstruction. When the ability of 16-row CT, first-generation 320-row CT (normal tube voltage), and second-generation 320-row CT (using a low tube voltage plus iterative image reconstruction) to detect myocardial fibrosis was evaluated by comparison with cardiac MRI, it was found that the second-generation 320-row CT had the highest diagnostic performance and showed improved site-specific sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy at 73%, 97%, 85%, 95%, and 93%, respectively.[1096]

### e. Indications

The 2010 Guideline for the Appropriate Use of Cardiac CT states that because radiation exposure and use of contrast medium are inherent disadvantages of CT, it is inappropriate as the first choice for follow-up of myocardial infarction and assessment of LV function in patients with heart failure.[484] Nevertheless, if adequate images cannot be obtained by TTE or cardiac MRI because of technical problems, CT is appropriate for follow-up of myocardial infarction or evaluation of LV function in heart failure patients. This is largely due to progress in CT scanners, such as improvement of temporal resolution by dual-source CT and the emergence of 320-row CT enabling clear cardiac imaging even in patients with arrhythmia, as well as advances in workstations and analytical software. In patients with new-onset heart failure, assessment of the coronary arteries by CT to estimate the etiology is divided into 6 categories depending on the risk of coronary heart disease and the LVEF. According to this classification, coronary artery evaluation by CT is only "appropriate" if the LVEF is decreased and the risk of coronary heart disease is low or moderate; otherwise the appropriateness of CT is "inconclusive."

### f. Other Applications

During evaluation of LV function, CT is useful for examining the LV apex, which is difficult to observe by TTE. Particularly, it is considered that the accuracy for detection of apical thrombus, which occurs frequently in patients with LV apical hypokinesia, is higher with CT than TTE. Although the increase in radiation exposure associated with retrospective ECG gating is a disadvantage of CT, it is possible to reduce radiation exposure by tube current dose modulation, which involves increasing the tube current from end-systole to end-diastole and decreasing the current during the other phases of the cardiac cycle. Although image quality is reduced for the phase with lower tube current, evaluation of wall motion is still possible. With regard to assessing LV function, not only the LVEF, but also regional LV wall motion can be determined, and the accuracy of evaluating myocardial viability can be improved by combined assessment of the extent of LV systolic thickening, the presence/absence of low CT values in the LV myocardium, and information on the coronary arteries. As noted above, additional late-phase imaging with prospective ECG gating can also detect areas of myocardial fibrosis and inflammation with minimal additional radiation exposure, but this requires injection of more than the usual 50 mL of contrast medium.

If the LV volume is measured at each phase of the cardiac cycle after dividing it into 20 parts, an LV volume curve can be drawn, and, theoretically, LV diastolic function can be determined from this LV volume curve. However, even dual-source CT, which has the best temporal resolution currently, only has a temporal resolution of about 75 ms and is inferior to TTE or invasive left ventriculography (LVG).

Therefore, volume measurement is unreliable, especially in the fast-moving phases of the cardiac cycle, and the LV volume curve obtained by CT is considered to differ from the true volume curve, making it difficult to assess LV

diastolic function at present. As a potential new development for the evaluation of myocardial viability in the future, it may become possible to perform the same examinations as with cardiac MRI, such as assessment of myocardial extra cellular volume in patients with heart failure, by using spectrum CT to measure the myocardial iodine content.

### 3.1.6 Cardiac Catheterization and Invasive LVG

#### a. Methods

In patients with coronary heart disease undergoing cardiac catheterization, myocardial viability is assessed by invasive LVG. Transarterial invasive LVG is performed and moving images of the heart are recorded. Information on LV volume, LVEF, and regional LV wall motion is also obtained.

#### b. Interpretation of the Findings and Relationship With Disease

Regional wall motion on invasive LVG reflects myocardial contractility, and wall motion is visually assessed according to the AHA classification as normokinesis, hypokinesis, akinesis, or dyskinesis. As a method for quantitatively evaluating LV wall motion abnormalities, the centerline method is used widely and provides excellent quantitative data.[1099] Preservation of wall motion on invasive LVG is proof of myocardial viability. However, it is difficult to judge myocardial viability in patients with severely abnormal LV wall motion associated with myocardial stunning after prolonged ischemia or hibernating myocardium due to chronic ischemia.

Regardless, areas where LV wall motion improves due to PESP are considered to be viable.[1100,1101] It should be noted that the absence of PESP does not always indicate lack of viability, and that improvement of LV wall motion due to PESP varies with the cardiac load.[1102] When determining myocardial viability from the improvement in LV wall motion with nitrate administration,[1103] the same caution is required as for the evaluation of PESP. It is difficult to assess myocardial viability based on the severity of coronary artery stenosis and coronary blood flow. The extent of collateral flow on coronary angiography often influences LV viability.

#### c. Features, Advantages, and Disadvantages

The greatest advantages of invasive LVG are that, different from TTE, it provides high-resolution images in all patients and the orientation of observation is constant. However, evaluation may be difficult due to inadequate imaging or arrhythmia. The disadvantages are that it is an invasive test and observation of LV wall motion under different loading conditions requires multiple imaging sessions unless biplane equipment for simultaneous imaging from 2 directions is used.

#### d. Indications and Contraindications

Invasive LVG is indicated for patients with suspected coronary heart disease. However, given the potential complications owing to its invasive nature, it is only indicated when the benefits of the information that can be obtained clearly outweigh the potential risks. TTE is preferred for the evaluation of LV wall motion before and after stress loading.

## 3.2 Criteria for Selecting Tests

One of the most significant reasons for assessing myocardial viability is to predict the outcome of revascularization in patients with myocardial infarction. In patients with old myocardial infarction, a variety of imaging modalities are used to assess myocardial viability before deciding on the indication for revascularization. Even in patients with reduced regional LV wall motion, viable hibernating myocardium may still exist, and, therefore it is necessary to assess viability by performing stress TTE with low-dose dobutamine or myocardial blood flow imaging with exercise or pharmacological stress. At facilities with PET equipment, FDG-PET can be used as the gold standard.

Assessment of viability based on late enhancement and evaluation of LV wall motion has been applied clinically using cardiac MRI and CT in recent years. The absence of LV wall motion after severe transient myocardial ischemia, especially after revascularization, should be examined, because of the potential presence of viable stunned myocardium, and myocardial contrast TTE is also useful in such cases.

Observational studies have suggested that revascularize-

**Table 53. Meta-Analyses Assessing Detectability (%) of Hibernating Myocardium**

| No. of studies in each meta-analysis | Total no. of patients | Diagnostic test | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) |
|---|---|---|---|---|---|---|
| 41 studies | 1,421 | Dobutamine stress echocardiography | 82 | 80 | 77 | 85 |
| 40 studies | 1,119 | Tl-201 SPECT | 87 | 55 | 64 | 81 |
| 25 studies | 721 | Tc-99m sestamibi SPECT | 81 | 66 | 71 | 77 |
| 24 studies | 756 | $^{18}$F-FDG-PET | 93 | 58 | 51 | 86 |
| 13 studies | 420 | End-diastolic wall thickness on MRI | 95 | 41 | 56 | 92 |
| 13 studies | 420 | Dobutamine stress MRI | 74 | 82 | 78 | 78 |
| 13 studies | 420 | Late gadolinium enhanced MRI | 84 | 63 | 72 | 78 |

Data were averaged by the number of patients. All studies defined hibernating myocardium on the basis of improved wall motion after recanalization. (Reproduced from Schinkel et al. 2007,[301] with permission.)

| Table 54. Recommendations and Levels of Evidence for Testing Methods to Evaluate Myocardial Viability | | | | |
|---|---|---|---|---|
| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
| Radionuclide imaging to evaluate myocardial viability when determining the indications for revascularization in asymptomatic patients with coronary heart disease | I | B | B | III |
| Noninvasive imaging (radionuclide imaging, cardiac MRI, stress echocardiography, etc.) to evaluate myocardial ischemia and viability in patients with new-onset heart failure who have coronary heart disease without angina pain and no contraindications to revascularization | IIa | C | B | III |
| Cardiac MRI and stress echocardiography before revascularization in patients with heart failure who have coronary heart disease and are candidates for revascularization | IIa | B | B | III |
| $^{18}$F-FDG-PET to assess the prognosis and extent of salvageable myocardium in patients with coronary heart disease and severe left ventricular dysfunction before selecting coronary revascularization or heart transplantation | I | B | B | III |
| $^{18}$F-FDG-PET in patients with moderate or severe fixed perfusion defects or in whom other tests have not been diagnostic | I | B | B | III |
| $^{18}$F-FDG-PET to assess the prognosis and extent of salvageable myocardium in patients with coronary heart disease and moderate left ventricular systolic dysfunction before selecting coronary revascularization or heart transplantation | IIa | B | B | III |
| Late gadolinium enhancement and dobutamine stress cardiac MRI to predict improvement of cardiac function after revascularization in patients who have severe left ventricular dysfunction and ischemic cardiomyopathy with akinetic regions | I | B | B | III |
| Late gadolinium enhancement and dobutamine stress cardiac MRI to estimate the outcome of revascularization in patients with moderate or severe left ventricular dysfunction | IIa | B | B | III |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

tion of hibernating myocardium may improve survival and LV function,[1079,1104,1105] but selection bias of patients receiving CABG has been a particular concern because the studies were not randomized. A meta-analysis of 24 nonrandomized studies (mean LVEF, 32%; n=3,088) on evaluation of myocardial viability before revascularization in patients with coronary heart disease and LV dysfunction[306] indicated an 80% reduction of annual mortality compared with drug therapy after revascularization in patients with viable myocardium. However, no significant improvement was observed after revascularization in patients without viable myocardium.[1106]

Meta-analysis results reporting the ability to detect hibernating myocardium by the main testing modalities is shown in **Table 53**.[301] There was improvement of LV wall motion after revascularization regardless of the definition of hibernating myocardium. As seen in **Table 53**, the ability to detect hibernating myocardium is excellent. With regard to sensitivity, the LV end-diastolic wall thickness on FDG-PET and cardiac MRI is particularly good, and dobutamine stress TTE and dobutamine stress cardiac MRI show excellent specificity. For the prediction of recovery of LV wall motion, Nishimura et al reported that the sensitivity and specificity were 80% and 60%, respectively, with Tl-201 or Tc-99m SPECT, and 90% and 65%, respectively, with FDG-PET.[1107] Therefore, it is recommended to consider the contraindications of each diagnostic test, as well as the detectability characteristics when deciding which method to use.

As stated in previous guidelines on assessment of myocardial viability,[306,307,311,1067,1108–1115] it is important to adhere strictly to the objectives of imaging for each target disease; that is, "myocardial viability should be assessed prior to coronary revascularization in patients with heart failure and coronary heart disease to determine the treatment strategy."

**Table 54** lists the level of evidence for each test based on the data currently available.

## 4. Assessment of Cardiac Function

Cardiac function of patients with chronic coronary heart disease is assessed by echocardiography, radionuclide imaging, cardiac CT, cardiac MRI, or cardiac catheterization/ventriculography. Evaluation of cardiac function should be performed when coronary heart disease is strongly suspected, when new-onset heart failure or arrhythmias are noted, and when the treatment strategy needs to be changed, and it is also important for predicting the prognosis.[121,122] An appropriate test should be chosen from among the various imaging modalities by taking into account the risks, benefits, contraindications, radiation exposure, and cost.[505] This section mainly focuses on selection of noninvasive diagnostic imaging methods according to the disease state.

### 4.1 Assessment of Cardiac Function in Chronic Coronary Heart Disease (Table 55)

#### 4.1.1 Echocardiography

Echocardiography is frequently used to assess cardiac function because it is noninvasive, simple, rapid, easy to repeat, safe, and low cost.[128,1116–1119] It is widely used at the bedside, in the emergency room, and in the operating room. Cardiac function is often normal in patients with chronic coronary heart disease, but echocardiography is useful for detecting regional wall motion abnormalities and for differentiation from other conditions that cause chest pain, such as aortic stenosis. It is particularly useful if the patient has a heart murmur, a history of myocardial infarction, or signs of heart failure.[127,128] When transthoracic echocardiography is performed, right and left ventricular systolic and diastolic function is evaluated by using 2- or 3-dimensional echocardiography, pulsed and continuous Doppler, color Doppler, tissue Doppler, and strain analysis.

The LVEF is obtained by the modified Simpson's method,[1117] in which the end-diastolic and end-systolic left ventricular volumes are calculated by tracing the endocar-

**Table 55. Recommendations and Levels of Evidence for Testing Methods to Evaluate Cardiac Function**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **Echocardiographic evaluation of left ventricular function** All patients with suspected chronic coronary heart disease at initial presentation | I | B | B | IVa |
| **Echocardiographic evaluation of left ventricular function** Patients with OMI, abnormal Q waves, signs of heart failure, complex ventricular arrhythmias, and undiagnosed cardiac murmur | I | B | A | IVb |
| **Evaluation of cardiac function by electrocardiogram-gated SPECT** Assess left ventricular volumes and LVEF when echocardiographic evaluation is difficult | IIa | C | B | IVb |
| **Evaluation of cardiac function by cardiac MRI** If echocardiographic evaluation is difficult and assessment of right ventricular function is necessary | I | C | A | IVb |
| **Cardiac CT** If evaluation by other noninvasive methods is difficult | I | C | B | IVb |
| **Left ventriculography** Patients undergoing coronary angiography | IIa | B | B | III |
| **Invasive measurement of pulmonary artery pressure and measurement of cardiac output** Patients with heart failure and circulatory failure if clinical evaluation is inadequate | I | C | B | IVb |
| **Invasive measurement of pulmonary artery pressure and measurement of cardiac output** Routine assessment of treatment-responsive normotensive patients with heart failure | III | B | D | II |
| **Evaluation of left heart function by echocardiography, cardiac radionuclide imaging, cardiac MRI, or cardiac CT** Routine assessment in patients with a normal ECG, no history of myocardial infarction, no signs of heart failure, and no complex ventricular arrhythmias | III | C | C2 | VI |
| **Routine evaluation of left heart function after <1 year by echocardiography, cardiac radionuclide imaging, cardiac MRI, or cardiac CT** Patients with no changes in clinical condition or treatment | III | C | C2 | VI |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

dial contour in the apical 4-chamber view (and 2-chamber view for the biplane Simpson's method). The Teichholz method,[1120] in which left ventricular inner diameter shortening is calculated from measurement of the left ventricular internal dimension at end-diastole and end-systole, is inaccurate in patients with left ventricular wall motion abnormality or remodeling and is not recommended in such patients. Measurement of the left ventricular volume and LVEF by 3D echocardiography is as accurate as by cardiac MRI.[1121] The Doppler method allows calculation of the stroke index and cardiac output. In recent years, evaluation of systolic function by tissue Doppler and strain analysis has shown high reproducibility, and even detection of slight cardiac dysfunction is possible.[1122] Left ventricular diastolic function cannot be evaluated accurately by a single echocardiographic index and is therefore evaluated from a composite index. Left ventricular diastolic dysfunction is the first sign of myocardial ischemia and suggests microangiopathy in patients who complain of shortness of breath and chest pain.[133,1123] Evaluation of right ventricular function by echocardiography is relatively easy for tricuspid annular plane systolic excursion (TAPSE) and the tricuspid annular lateral systolic velocity (S') measured by tissue Doppler imaging.[1117,1124]

### 4.1.2 Cardiac Radionuclide Imaging

Evaluation of cardiac function by cardiac radionuclide imaging with ECG-gated myocardial perfusion SPECT is performed using dedicated software for analysis of cardiac function. LVEF is assessed from the ventricular volume, and diastolic function is assessed from the differential volume curve.

The reproducibility of cardiac function indices calculated from ECG-gated SPECT is high. During stress radionuclide imaging, transient left ventricular enlargement and a decrease in LVEF may be noted; these changes reflect transient myocardial ischemia and aid in the diagnosis of coronary heart disease without blood flow evaluation. In patients who cannot undergo exercise testing, a pharmacological stress test is performed. Adenosine is commonly used, but may induce bronchospasm in patients with asthma. In such patients, dobutamine or regadenoson (a selective $A_{2A}$ receptor agonist; not covered by health insurance)[1125] should be used instead. ECG-gated SPECT is useful for evaluating cardiac function, but has the disadvantage of radiation exposure. Cardiac blood-pool scintigraphy can evaluate both left and right ventricular function, and may be used when it is difficult to perform evaluation by ECG-gated SPECT.

### 4.1.3 Cardiac MRI

The advantages of cardiac MRI are that it is not affected by bone or air and can capture moving images of the heart with high spatial resolution in any plane in any direction. Accurate measurement of left ventricular function can be performed in patients with myocardial infarction and left ventricular deformity and/or wall motion abnormality. Cardiac MRI is currently the most accurate modality for measuring left ventricular and right ventricular volumes, cardiac mass, and LVEF.[1126–1129] When evaluation by echocardiography is difficult, cardiac MRI is the best alternative, especially for evaluating the right ventricle.[608] LGE imaging with gadolinium contrast medium can identify myocardial fibrosis, and the distribution of the LGE helps to distinguish between ischemic and nonischemic myocardium and to assess myocardial viability.[939,1127,1130]

### 4.1.4 CT

When cardiac function is evaluated with ECG-gated

MDCT, accurate measurement of left and right ventricular volumes, cardiac mass, and LVEF is possible, as with cardiac MRI.[1131–1133] Assessment of cardiac function by cardiac MRI is the standard procedure to combine with CCTA, because cardiac MRI allows detailed measurement of cardiac function by ECG-gated image reconstruction without increasing the use of contrast medium or radiation exposure,[1134] but CT evaluation has been less common because of the disadvantage of increased radiation exposure. However, cardiac MRI is expensive and imaging takes a long time, so the number of facilities where it is available remains limited.[1131] Cardiac MRI is relatively contraindicated in patients with claustrophobia, pacemakers, or ICDs, and analysis of cardiac function by CT is useful in such patients.[1135]

#### 4.1.5 Cardiac Catheterization and Ventriculography

Catheterization and ventriculography were previously considered the gold standards, but in recent years noninvasive methods such as cardiac MRI (which excels in quantitative assessment) have frequently been used to measure left ventricular function.

As an index of systolic function, biplane left ventriculography (LVG) is used to measure LVEF and assess regional wall motion.[1136–1140] The papillary muscles and trabeculae are within the contour of the left ventricular cavity on LVG. Accordingly, the calculated value tends to be an overestimation compared with the true luminal volume. In a study comparing LVG and cardiac CT with cardiac MRI as the standard, cardiac CT was more accurate than LVG for assessing global and regional left ventricular wall motion.[1141] Impedance catheters do not require contrast medium and can be used to measure left ventricular volume and LVEF.[1142,1143] Cardiac output can also be measured by thermodilution. In addition to LVEF, dP/dt is another index of contractility. (dP/dt)/P is also used, which is obtained by adjusting for the effect of changes in preload and afterload.[1144] The left ventricular stroke work can also be calculated from the pressure–volume curve. Indices of diastolic function include dP/dt obtained from measurement of left ventricular pressures using a catheter tip manometer and the time constant of left ventricular relaxation (T or $\tau$).[1145–1147]

### 4.2 Application to Chronic Coronary Heart Disease

#### 4.2.1 Assessment of Resting Cardiac Function

Echocardiographic assessment of cardiac function is important for risk stratification of patients with chronic coronary heart disease, and it should be performed at the initial presentation of all patients with suspected chronic coronary heart disease.[127]

Echocardiographic assessment of cardiac function is recommended for patients with chronic coronary heart disease who have OMI, abnormal Q waves, signs of heart failure, complex ventricular arrhythmias, or an undiagnosed heart murmur.[121,127,640,1148] It was reported that when resting LVEF was <35%, the annual mortality rate was >3%.[1149] Echocardiography enables evaluation of left ventricular systolic and diastolic dysfunction, as well as left ventricular morphology, and may allow determination of the etiology of heart failure. In patients without signs of left ventricular dysfunction, it is possible to evaluate left ventricular and left atrial enlargement and to determine the cause of chest pain due to noncoronary heart diseases, such as aortic stenosis, so that treatment indices can be selected and prognostic information can be obtained. It is also possible to estimate the pulmonary artery pressure, evaluate mitral regurgitation, identify left ventricular aneurysms, and detect left ventricular thrombi. Thus, echocardiography is useful for predicting the prognosis.[640]

On the other hand, assessment of cardiac function by radionuclide imaging or cardiac MRI can be considered in patients with OMI, abnormal Q waves, signs of heart failure, or complex ventricular arrhythmias who do not require evaluation of an undiagnosed cardiac murmur.[640,1150,1151]

Cardiac MRI is accurate for assessing ventricular function and also provides information on the morphology of the myocardium and heart valves. LGE MRI can identify undetected necrotic scars and viable myocardium.[939,1152,1153] Evaluation of cardiac function by cardiac CT is also useful. However, these 3 modalities mentioned are all more expensive than echocardiography. Although attempts have been made to reduce radiation exposure during cardiac CT and cardiac radionuclide imaging, these methods are still not recommended for patients with a low pretest probability of coronary heart disease or for adolescents.

Left ventriculography is indicated when evaluation by other modalities is considered difficult in patients who require coronary angiography.[1154] Invasive measurement of the pulmonary artery pressure and cardiac output are recommended when clinical evaluation is inadequate in patients with combined heart failure and circulatory failure,[1155,1156] but their routine use is not recommended in normotensive patients with heart failure who respond to treatment.[1157,1158]

In patients with normal ECG, long-term repeated assessment of cardiac function with echocardiography, cardiac radionuclide imaging, cardiac MRI, or cardiac CT is not recommended, provided they do not have OMI, no signs of heart failure, and no complex ventricular arrhythmias.[640] Also, periodic evaluation at intervals of less than 1 year is not recommended for patients with no changes in clinical manifestations or treatment strategy.

#### 4.2.2 Assessment of Cardiac Function With Stress Loading

##### a. If Exercise Can Be Performed

If exercise is possible but the ECG findings are nondiagnostic, assessment of cardiac function by cardiac radionuclide imaging or echocardiography is recommended.[640,1150,1159–1163] If the patient has left bundle branch block or ventricular pacing, exercise/pharmacological stress radionuclide imaging or echocardiography is recommended.[1164,1165]

##### b. If Exercise Is Impossible

Pharmacological stress radionuclide imaging or echocardiography is recommended for patients with chronic coronary heart disease who cannot perform adequate exercise, irrespective of whether ECG changes are diagnostic or not.[640,1150,1159]

#### 4.2.3 Cardiac Function Assessment During Regular Follow-up

Assessment of cardiac function using echocardiography or radionuclide imaging is recommended for patients with signs of the onset/progression of heart failure or for patients with a history of interventions for myocardial infarction.[640] However, regular cardiac function assessment using echo-

cardiography or radionuclide imaging is not required in patients with no changes in clinical condition and who have a low risk of cardiovascular events.[128]

#### 4.2.4 Follow-up of Patients With Asymptomatic Myocardial Ischemia

Follow-up evaluation at intervals of 2 years or longer using exercise/pharmacological stress radionuclide imaging, echocardiography, or cardiac MRI is useful in patients with a history of asymptomatic myocardial ischemia, providing there is a high risk of recurrent cardiac events, inability to perform adequate exercise, nondiagnostic ECG changes, or incomplete coronary revascularization. Follow-up evaluation using exercise/pharmacological stress radionuclide imaging, echocardiography, or cardiac MRI is not required within 5 years after CABG or within 2 years after PCI.[128,316,1115]

### 4.3 Future Challenges

In the nuclear cardiology field, assessment of cardiac function is not only possible with SPECT but also PET, enabling accurate evaluation by various modalities such as cardiac MRI and cardiac CT. In addition, assessment of cardiac function by 3-dimensional echocardiography has equal accuracy to these modalities and strain analysis, such as speckle tracking, can detect even a slight decrease in cardiac function at an early stage. In the future, it will be important to select these modalities appropriately by considering the risks, benefits, and cost-effectiveness, after evaluating the patient's clinical condition and pretest probability.

## 5. Prediction of Prognosis

In the Framingham heart study, the annual mortality rate for chronic coronary heart disease was 4%.[1166] In a registry study of 38,602 patients performed between 2003 and 2004 after aspirin, $\beta$-blockers, and statins had been introduced, the 1-year mortality rate was 1.9% and the combined rate of cardiovascular death, myocardial infarction, and stroke was 4.5%.[1167] The mortality rate for coronary heart disease is lower in Japan than in many other countries, but it is currently increasing, unlike in the USA where the rate is decreasing.[1168] Against this background, the clinical significance of each test for predicting prognosis is described in this section, based on overseas evidence and Japanese data.

### 5.1 Clinical Signs

The history and physical findings can be used to predict the prognosis with no additional costs or additional risks to the patient. The presence of angina at rest, new-onset angina, worsening of angina, or dyspnea adds to the risk of death or myocardial infarction.[1169] Among 5,712 patients with chronic coronary heart disease who underwent stress testing, the annual mortality rate was 2.4% for patients who had angina without dyspnea vs. 6.4% for patients who had dyspnea.[1170] The incidence of cardiovascular events is high in patients with physical signs of heart failure and in patients with arteriosclerotic lesions of vessels other than the coronary arteries (carotid and lower limb arteries).[1167]

### 5.2 Risk Scores

Risk scores are lower in patients with chronic coronary heart disease than in those with ACS. A clinical study of lipid-lowering therapy showed that risk stratification could be performed by age, sex, smoking, OMI, diabetes mellitus, hypertension, prior revascularization, total cholesterol, and HDL-cholesterol.[1171] In Japan, the Suita score has been reported, which stratifies the 10-year risk of developing coronary heart disease by scoring the age, sex, smoking, blood pressure, HDL-cholesterol, LDL-cholesterol, glucose intolerance, and family history of early-onset coronary heart disease.[1172]

### 5.3 Biochemical Tests

According to the AHA and CDC statements on inflammatory markers and cardiovascular disease, the established prognostic markers are total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, fasting glucose, and renal function (eGFR).[1173] In addition, high-sensitivity C-reactive protein,[1174] BNP,[1175] and troponin[1176] have been attracting attention as new biomarkers.

### 5.4 Exercise ECG

Exercise ECG is not only useful for diagnosing myocardial ischemia, but also for predicting prognosis. The ACC/AHA Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease states that patients with ST depression ≥2 mm, stress-induced ST elevation, or induction of lethal arrhythmias by low stress are high risk and have an annual incidence of death or myocardial infarction ≥3%, while patients with symptomatic ST depression ≥1 mm are intermediate-risk and have an annual incidence of death or myocardial infarction ranging from 1% to 3%.[640] The most important prognostic factor is the maximum tolerated exercise load, not the duration of exercise or occurrence of symptoms, and it is reportedly associated with the vital prognosis.[1177]

### 5.5 Echocardiography

Impairment of left ventricular function is reported to be an adverse prognostic factor. According to the ACC/AHA Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease, patients with an LVEF <35% and coronary artery disease represent a high-risk group with an annual incidence of death or myocardial infarction ≥3%, while patients with an LVEF of 35–49% and coronary artery disease represent an intermediate-risk group with an annual incidence of death or myocardial infarction ranging from 1% to 3%.[640] Detection of impaired regional wall motion and left ventricular dysfunction on stress echocardiography is reported to be an adverse prognosis factor.[1163] On the other hand, if stress echocardiography shows no abnormal findings, the annual incidence of cardiovascular events is <1%.[1178]

### 5.6 Cardiac Radionuclide Imaging

#### 5.6.1 Myocardial Perfusion SPECT

Many observational studies have shown that stress myocardial perfusion scintigraphy is useful for predicting the prognosis of coronary heart disease.[1179] As the amount of

ischemic myocardium detected by stress myocardial perfusion SPECT becomes more extensive, there is a proportional increase in cardiovascular events, whereas prognosis is excellent with drug therapy if ischemia is negative.[227] The indicators of a poor prognosis on stress myocardial perfusion SPECT include: (1) severe and extensive reduction of blood flow (affecting ≥20% of the left ventricular myocardium),[1180] (2) transient or persistent dilation of the left ventricular cavity,[1181] and (3) decreased LVEF and increased ESV on ECG-gated SPECT. In a study of 5,183 patients who underwent stress myocardial perfusion SPECT, the 2-year incidence of cardiac death and myocardial infarction was 0.7% per year in 2,496 patients without defects, which was lower than the incidence of 2.6% per year in patients with defects.[276] In addition, a study of 309 patients with suspected coronary heart disease and normal exercise perfusion imaging showed that cardiac death only occurred in 1% of them during a 10-year period.[1182]

The J-ACCESS study was a prospective cohort study of 4,031 patients who underwent ECG-gated stress myocardial perfusion SPECT and were followed for 3 years.[223] Subsequently, the J-ACCESS 2 study was performed in 506 high-risk patients with asymptomatic type 2 diabetes mellitus,[288] the J-ACCESS 3 study enrolled 431 patients with CKD,[1183] and the J-ACCESS 4 study followed 494 patients who underwent stress scintigraphy before and after revascularization.[287] The J-ACCESS study showed that the incidence of events was much lower in Japanese patients (≈1/3) than in Western patients (4.3% over 3 years).[223] Particularly, the incidence of events was extremely low in patients with normal stress ECG-gated SPECT (0.81% per year in patients with normal myocardial blood flow, 0.67% per year in patients with normal myocardial blood flow+ normal ESV, and 0.61% in patients with normal myocardial blood flow+normal ESV+normal LVEF), indicating that normal findings on stress ECG-gated SPECT were associated with an extremely good prognosis.[1184] It was also reported that a negative result on stress ECG-gated SPECT is associated with a good prognosis, regardless of the pretest probability.[1185]

The J-ACCESS study showed that an LVEF ≤45%, summed difference score (SDS) ≥2, age, history of revascularization, and diabetes mellitus were independent predictors of cardiovascular events.[1186] These factors have also been reported as useful for predicting the onset of heart failure.[1187] Furthermore, Yoda et al found a strong association between the severity of ischemia and cardiovascular events in Japanese patients in a single-center study.[1188] Data from the J-ACCESS study were used to develop a risk model for the Japanese population, which allows the incidence of events to be predicted from the age, sex, diabetes mellitus, presence/absence of CKD, ischemic myocardial volume on SPECT, and the LVEF and ESV obtained from ECG-gated SPECT.[1189,1190]

### 5.6.2 Fatty Acid Metabolism Imaging

In Japan, I-123 BMIPP imaging is covered by health insurance, and has been shown to have prognostic value. Zen et al reported that BMIPP imaging was a significant prognostic indicator in 677 patients with asymptomatic diabetes mellitus and PAD,[449] and Nishimura et al identified an association between cardiac death and abnormal BMIPP accumulation in dialysis patients without obstructive coronary heart disease.[1191] Moreover, Hashimoto et al reported that the severity of the BMIPP defect could predict the prognosis of patients with nonischemic heart failure and preserved left ventricular systolic function.[1192]

### 5.6.3 Sympathetic Nerve Imaging

There have been many reports about the prognostic value of I-123-labeled MIBG. Nakata et al combined information from independent heart failure databases in Japan and identified an association between MIBG findings and prognosis in 1,322 patients with heart failure. Also, the heart-to-mediastinum ratio on MIBG imaging has been shown to be an independent predictor of fatal events, independent of the NYHA classification, LVEF, and BNP level.[389]

### 5.6.4 Evaluation of CFR by PET

Measurement of the CFR by PET is the gold standard for assessment of myocardial ischemia.[1193] CFR has been reported to be a prognostic indicator that is independent of defect severity, cardiac function, and CACS.[476,1194]

## 5.7 Cardiac CT

### 5.7.1 CACS

The CACS is known to be useful for stratifying the risk of cardiovascular events. According to the ACC/AHA consensus document, investigation of 27,622 asymptomatic patients showed that the relative risk was increased by 4.3-fold in the case of CACS 100–400, by 7.2-fold if the CACS was 401–900, and by 10.8-fold if the CACS was ≥1,000.[1195] The annual incidence of cardiac events was 0.1% if the CACS was 0, 0.5% if the CACS was 1–100, and 2.4% if the CACS was ≥100.[1196] Thus, the CACS is useful for risk stratification of asymptomatic, intermediate-risk patients. On the other hand, there have been few reports about the prognostic value of the CACS in symptomatic patients. In 3,924 patients with a CACS of 0, cardiovascular events occurred in 1.8% during a mean follow-up period of 42 months, while 8.9% of CACS-positive patients developed events.[1197] Currently, many guidelines recommend using the CACS for risk assessment in intermediate-risk or low-risk patients who have diabetes mellitus or a family history of early-onset coronary heart disease.

### 5.7.2 CCTA

CCTA is the most widely used imaging modality in Japan. Advances in CT equipment have reduced radiation exposure and improved image quality, and many current clinical and diagnostic guidelines recommend CT-based diagnosis.[486] Information obtained from CCTA includes the presence/absence of coronary artery stenosis,[1198] assessment of plaque characteristics,[1199] and assessment of ischemia by FFR-CT based on hydrodynamics and advanced computing.[1200]

The number of coronary vessels with stenosis, the number of plaques, and the plaque characteristics on CT have been used to predict the short-term prognosis as well as for predicting the long-term prognosis over 5 years or longer.[537,1201,1202] Feutcher et al studied CCTA findings in 1,499 patients with long-term follow-up for an average of 7.8 years, and demonstrated a strong association between the severity of stenosis or plaque characteristics and the prognosis.[1203] The relationship between FFR-CT, which uses advanced computing to calculate the FFR from CT images, and the long-term prognosis has not been clarified, but FFR-CT is expected to play a role as a gatekeeper for catheter examinations in the future.[588,1204,1205] However,

further studies are needed to determine whether the long-term prognosis can be predicted.

## 5.8 Cardiac MRI

Detection of asymptomatic myocardial injury by LGE MRI has been shown to be useful for evaluating the prognosis of patients with ischemic heart disease. In patients with suspected ischemic heart disease and no history of myocardial infarction, Kwong et al reported that the presence or absence of LGE MRI was the strongest predictor of cardiac death or major adverse events, even after adjustment for other risk factors such as diabetes mellitus.[598,1206] Stress myocardial perfusion MRI has been shown to be useful for diagnosing ischemic heart disease in patients with chest pain and for predicting the future risk of ischemic heart disease, myocardial infarction, or cardiac death.[600,602] Jahnke et al[601] performed adenosine and dobutamine stress myocardial perfusion MRI in patients with ischemic heart disease and found a significantly higher incidence of cardiac death and nonfatal myocardial infarction (16.5% over 3 years) in the case of both tests being abnormal. In addition, cardiac death or acute myocardial infarction was at least 3-fold more likely in patients with abnormal results for both stress myocardial perfusion MRI and LGE MRI, while patients with negative results for both tests had a cardiac event-free rate of 98.1% per year.[1207]

## 5.9 Coronary Angiography

It is well known that the number of affected coronary vessels and left ventricular function influence the prognosis of patients with ischemic heart disease.[1208] The 5-year survival rate of patients with stenosis of the proximal left anterior descending artery is 90%, which is lower than that of patients with distal stenosis (98%).[1209] The SYNTAX score, obtained by adding lesion morphology to these items, is useful for selecting the optimal revascularization method.[1210] Patients with severe stenosis of the left main trunk, proximal left anterior descending artery, or left circumflex artery have a poor prognosis with medical therapy alone.

Coronary angiography provides anatomical information on the coronary arteries and is therefore useful for predicting the prognosis, but this method cannot assess the presence/absence of ischemia. Moreover, the extent of stenosis is determined relative to the proximal vessel as a control, so it is underestimated in patients with diffuse arteriosclerosis. It is also known that rupture of vulnerable plaque causing ACS (which affects survival), can occur at sites with <50% stenosis on coronary angiography. Thus, prediction of the prognosis by using the FFR and IVUS has attracted attention in the hope of overcoming these limitations of coronary angiography.

## 5.10 FFR

The FFR is an index of the functional severity of stenosis and is used to determine the indication for coronary revascularization.[568,711] It shows the severity of stenosis at the time of examination and does not predict subsequent progression or destabilization of the lesion. However, in patients with chronic stable coronary heart disease, lesions that are negative for ischemia as proven by FFR are associated with fewer subsequent events and a better prognosis.[733,734] The functional severity of stenosis detected by the FFR is not only influenced by the anatomical features of the lesion (lumen area, lesion length, and lesion morphology), but also by a number of other factors including the blood flow to the distal territory (i.e., the area perfused by the affected artery), the extent of collateral flow, and the presence of coronary microvascular obstruction and myocardial damage.[711] A lower FFR value indicates more severe ischemia.[1211,1212] The FFR value for predicting the occurrence of events, including coronary revascularization, is ≈0.8, but the value for predicting hard events (death and myocardial infarction) is lower, being ≈0.50–0.65.[735,736]

Approximately 15–20% of patients who undergo revascularization by PCI with stenting show little improvement in FFR, suggesting a poor prognosis after PCI.[1213,1214] Inadequate improvement in the FFR results from problems related to the target lesion, such as poor stent expansion and dissection at the stent edge,[1215] as well as the presence of diffuse disease. Inadequate improvement in FFR is relatively common in patients with left anterior descending artery lesions, and is reported to be associated with CKD.[1216] It may predict a poor prognosis independent of anatomical patency. It has been reported that the FFR value after stenting correlates with the FFR value before stenting;[1215] that is, a low FFR before treatment is a predictor of poor improvement in coronary blood flow by stenting. Determination of the FFR values for the 3 coronary arteries (3V-FFR) can be used to determine the total extent of functional myocardial ischemia. This method attempts to quantitatively evaluate the extent of coronary plaques by measuring the FFR in each of the 3 vessels and summing the values to

**Table 56. Recommendations and Levels of Evidence for Testing Methods to Predict Prognoses**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| Myocardial perfusion SPECT | I | A | A | I |
| $I^{123}$-BMIPP | IIb | C | C2 | IVa |
| $I^{123}$-MIBG | IIb | B | C2 | IVa |
| Myocardial perfusion PET | I | A | B | IVa |
| CACS | I | A | A | I |
| CTA (including plaque imaging) | IIa | A | B | II |
| FFR-CT | IIb | C | C1 | IVb |
| FFR | I | A | A | I |
| Stress ECG | I | C | B | IVb |
| Echocardiography | I | A | A | I |
| Cardiac MRI | IIb | C | C1 | IVb |
| Coronary angiography | I | A | A | I |
| IVUS | IIb | C | C1 | IVb |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

calculate the 3V-FFR, and it has been reported that 3V-FFR is a prognostic indicator of ischemia that is independent of FFR.[1217]

FFR is widely used clinically, but the invasive nature of this test limits the potential extent of usage. Evaluation of CFR by PET has recently become available and is also used to predict the prognosis.[313,1218] It has been reported that approximately 30% of patients show dissociation between the FFR and CFR when ischemia is evaluated.[1219] Importantly, patients with a low CFR have a poor prognosis due to the presence of diffuse lesions and microvascular obstruction, even if the FFR is good.[313,1218,1219]

### 5.11 IVUS

In the PROSPECT study,[1220] 697 patients with ACS underwent IVUS of 3 vessels, including a nonculprit vessel, and 11.6% of these patients had an event caused by rupture of plaque in the nonculprit vessel over a follow-up period of 3 years. Analysis by VH-IVUS showed that the presence of a thin fibrous cap, a lumen area $\leq 4.0\,mm^2$, and positive remodeling $\geq 70\%$ of the plaque were factors related to plaque rupture, with the incidence of events being higher in patients who had $\geq 2$ of these factors.

Recommendations and levels of evidence for prediction of prognosis are shown in **Table 56**.

## 6. Deciding the Treatment Strategy

Treatment of chronic coronary heart disease includes basal drug therapy and exercise therapy, as well as PCI and CABG for revascularization of the coronary arteries. Essentially, the indications for revascularization should be decided from the presence or absence of myocardial ischemia. However, it was reported that only 45% of elective PCI procedures involved advance evaluation of myocardial ischemia by stress testing.[1221] In fact, it is common that treatment is carried out on the basis of imaging findings alone in the actual clinical setting. The FAME study compared outcomes between patients with stable coronary heart disease and multivessel disease who underwent PCI for all significant organic stenoses vs. patients undergoing PCI for functional stenoses documented to cause myocardial ischemia, revealing a significant reduction of cardiovascular events in only the patients undergoing PCI for functional stenosis.[314]

According to this background, the importance of proving the presence of myocardial ischemia has recently been highlighted with respect to selection of the treatment strategy. It is important to decide the treatment strategy by considering improvement of QOL and the prognosis, after determining the range and extent of myocardial ischemia using various examinations. Because there are racial differences in the underlying disease pathology, treatment decisions should ideally be based on the results of reliable clinical research performed in Japan. However, sufficient results have not been obtained yet. Accordingly, this section describes the various tests that are useful when determining treatment strategies for chronic coronary heart disease by reviewing the results of large-scale clinical studies conducted overseas and some Japanese data.

### 6.1 Coronary Heart Disease Without Myocardial Infarction

#### 6.1.1 Principles of Deciding the Treatment Strategy

In patients with coronary heart disease who have good left heart function and no history of myocardial infarction, the range and extent of myocardial ischemia should be determined by various tests, and risk stratification should be performed from the prognostic perspective. The treatment strategy should be selected by considering the patient's comorbidities and age, such as whether to perform noninvasive treatment alone (including drug therapy) or invasive treatment, and whether to select PCI or CABG for invasive treatment. Progress in diagnostic imaging has been remarkable, leading to great improvement in the accuracy of evaluating coronary artery morphology by CT and MRA. Coronary angiography remains an essential procedure in the case of invasive treatment being considered. When the extent of stenosis is $\geq 75\%$ on coronary angiography, it is judged to be significant and invasive treatment should be considered. However, in principle, the treatment strategy should be decided after the presence of myocardial ischemia is verified by other methods.

#### 6.1.2 Significance of Tests Other Than Coronary Angiography for Selecting the Treatment Strategy

**a. Noninvasive Tests**

On exercise ECG, deep ST depression ($\geq 0.2\,mV$), a low exercise threshold for ST depression, and prolonged convalescent ST depression suggest severe myocardial ischemia. When the Duke treadmill score is calculated for prediction of the prognosis [(exercise duration) $-5\times$ (maximum ST depression mm) $-4\times$(chest pain index: 0 if chest pain is absent; 1 if chest pain is present; and 2 if chest pain is the reason for stopping exercise)], a score of $-11$ or lower indicates a high risk and a score of +5 or higher indicates a low risk.[5] However, it is impossible to identify the site of myocardial ischemia from the lead showing ST depression. In patients with bundle branch block, left ventricular hypertrophy, ventricular pacing, Wolff-Parkinson-White syndrome, or using digitalis preparations, there are limitations on determination of ST changes, with the sensitivity and specificity of exercise ECG being around 70%.[11]

Stress echocardiography and stress myocardial perfusion imaging allow the identification of regions of myocardial ischemia by detecting abnormal wall motion and myocardial perfusion abnormalities. According to the J-ACCESS study conducted in Japan, revascularization reduced cardiovascular events more effectively than drug therapy in patients with >10% of the myocardium affected by ischemia on myocardial perfusion imaging.[300] Pharmacological stress myocardial perfusion imaging with agents such as adenosine is useful in patients who find it difficult to perform exercise. Imaging of the myocardial sympathetic nerves (I-123-MIBG) and myocardial fatty acid metabolism (I-123 BMIPP) may identify regions of myocardial ischemia,[1222,1223] and these methods are particularly safe and useful in patients who have difficulty performing exercise. CCTA allows noninvasive morphological assessment of the coronary arteries and has increasingly been performed before coronary angiography in recent years. Its advantage is the ability to assess plaques and vascular remodeling as well as coronary artery stenosis.[1224] As evaluation becomes difficult when lesions have severe calcification, a method for removing calcification based on the difference from

noncontrast CT scans has been developed recently.[1225] Coronary MRA is not influenced by calcification, and it is possible to noninvasively evaluate coronary artery morphology without radiation exposure or use of contrast medium. Accordingly, widespread use of coronary MRA is expected in the future.[633]

#### b. Invasive Tests

IVUS is useful for assessing plaque morphology and is also an excellent modality for detecting calcification. It provides accurate information on the vessel diameter at the lesion and reference sites, as well as about plaque localization. Recently, tissue characterization by IVUS has become available for clinical use and has been applied to coronary plaques. OCT has higher resolution than IVUS and is particularly good for visualizing the lumen and vessel walls. Delineation of plaque rupture, erosion, and calcified nodules is possible, as well as quantification of the thickness of the fibrous cap.[1226] Angioscopy allows direct observation of the inside of a blood vessel, so the presence/absence of thrombus and the color of the vessel wall can be examined.[1227] Arteriosclerotic lesions are often yellow, whereas normal vessel walls are white. Albeit invasive, this intravascular imaging modality provides valuable information for determining the PCI strategy.

The CFR is an indicator of the maximal increase in coronary blood flow from the resting state. A CFR $\leq$2.0 suggests functional coronary artery stenosis, but the value is also influenced by microangiopathy resulting from conditions such as diabetes, cardiac hypertrophy, and myocardial infarction.[1228] The FFR is calculated as the pressure at the distal end of a stenosis during drug-induced vasodilation divided by the aortic pressure,[314] with FFR <0.75 indicating ischemia, 0.75–0.80 being borderline and FFR $\geq$0.80 is negative for ischemia. The DEFER study enrolled patients with an FFR $\geq$0.75 and compared outcomes between those with and without PCI after follow-up for 5 years. The incidence of cardiac death and myocardial infarction was 3.3% in the group without PCI and 7.9% in the group with PCI, confirming the absence of prognostic benefit from performing PCI.[733]

#### c. Predicting the Prognosis by Cardiac Radionuclide Imaging

Stress myocardial perfusion scintigraphy can assess the range and extent of myocardial ischemia without the use of contrast medium and a wealth of data are available on the prognostic implications. In patients with stress-induced ischemia affecting $\geq$10% of the left ventricular mass on stress myocardial perfusion scintigraphy, it was reported that revascularization significantly reduced cardiac death compared with drug therapy alone.[227] The J-ACCESS study[223,300] conducted in Japan showed that cardiovascular events increased according to the volume of ischemic myocardium, and the prognosis of patients with $\geq$10% ischemic myocardium was better after revascularization than with drug therapy alone. The LVEF calculated by ECG-gated SPECT was also useful for risk stratification. As more evidence has been obtained in Japan, it has become possible to evaluate the risk for individual patients by using Japanese data.[1229]

## 6.2 Old Myocardial Infarction

### 6.2.1 Assessment of Cardiac Function

In patients with OMI, assessment of cardiac function is important for predicting the prognosis and deciding treatment strategies.[1230] Resting echocardiography is excellent for assessing cardiac function, and can be performed quickly and easily. Resting echocardiography allows evaluation of regional wall motion, left ventricular systolic and diastolic function, and valvular function. In OMI patients, ventricular wall thinning, aneurysm formation, and the presence/absence of left ventricular thrombus or remodeling can be assessed. MRI and ECG-gated cardiac radionuclide imaging are superior to echocardiography for evaluating regional wall motion and cardiac function, but also for assessing myocardial viability (discussed next). Accordingly, use of these methods has been increasing in recent years.

### 6.2.2 Evaluation of Myocardial Viability

#### a. Stress Echocardiography

Evaluation of myocardial viability in the infarct zone is important for predicting the prognosis and determining the indications for invasive therapy to treat culprit lesions. Akinesis on resting echocardiography does not always indicate irreversible necrosis of the myocardium. If hibernating myocardium is present in the affected region, cardiac function may be improved by revascularization. Improvement of wall motion after low-dose dobutamine challenge indicates myocardial viability. When the diagnostic accuracy of dobutamine stress echocardiography for myocardial viability was investigated, the sensitivity and specificity were reported to be 74–87% and 73–86%, respectively.[1231] Because methods based on visual evaluation are dependent on the evaluator's subjective assessment and experience, objective evaluation methods such as tissue strain imaging are also being explored.

#### b. Cardiac Radionuclide Imaging

Myocardial perfusion SPECT with thallium or technetium is used to evaluate myocardial viability. In many reports, 50–60% of peak myocardial flow was used as the cutoff value for determining myocardial viability on the basis of resting myocardial blood flow.[1] Combined use with ECG-gated SPECT for evaluation of wall motion improves diagnostic performance. Myocardial perfusion PET has superior spatial resolution to SPECT and better diagnostic performance with qualitative imaging. PET can be performed with $^{18}$F-FDG to evaluate myocardial viability.[1] Myocardial blood flow can also be quantified, and CFR can be measured noninvasively using pharmacological stress.

#### c. MRI

LGE MRI achieves better contrast resolution than radionuclide imaging and can clearly delineate infarcted myocardium as high signal intensity areas.[1232] To perform stress myocardial perfusion MRI, coronary vasodilators such as adenosine are administered, and myocardial blood flow is assessed from the first-pass myocardial dynamics of gadolinium contrast medium. Cine MRI can be used to investigate regional wall motion by setting a cross-sectional view that is not affected by the lungs and other structures, allowing accurate evaluation of cardiac function. Thus, MRI can provide comprehensive assessment of the relationship between the ischemic/infarcted region and abnormal wall motion by comparing these various modalities.[939]

| Table 57. Recommendations and Levels of Evidence for Testing Methods of Selecting the Treatment Strategy | | | | |
|---|---|---|---|---|
| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
| **Coronary angiography** | | | | |
| Routine evaluation of patients with chest pain | III | C | D | VI |
| Morphological evaluation of stenosis in patients for whom revascularization is being considered | I | B | A | II |
| **CT** | | | | |
| Morphological evaluation of stenosis | IIa | B | B | IVa |
| **Exercise ECG** | | | | |
| Assessment of myocardial ischemia | IIa | B | B | IVa |
| **Echocardiography** | | | | |
| Evaluation of cardiac function and morphology | I | A | A | II |
| Evaluation of myocardial ischemia by stress loading | IIa | B | B | II |
| Evaluation of myocardial viability by stress loading | IIa | B | B | II |
| **Myocardial perfusion scintigraphy** | | | | |
| Evaluation of myocardial ischemia by stress loading | I | A | A | I |
| Evaluation of myocardial viability by stress loading | I | A | A | I |
| **FFR measurement** | | | | |
| Evaluation of myocardial ischemia | IIa | B | B | II |
| **Cardiac MRI** | | | | |
| Evaluation of cardiac function and morphology | IIa | C | B | IVa |
| Evaluation of myocardial ischemia by stress loading | IIb | C | C1 | IVb |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

### 6.2.3 Deciding the Treatment Strategy From Cardiac Autonomic Function

There is a strong relationship between the prognosis of patients with myocardial infarction or heart failure and the cardiac autonomic nervous system.[1233,1234] Evaluation of sympathetic nerve activity includes measurement of the blood and urine levels of catecholamines and quantitative assessment of cardiac sympathetic nerves by I-123 MIBG myocardial sympathetic nerve imaging (cardio-mediastinal ratio of radioactivity and the washout rate). Evaluation of parasympathetic nerve activity is based on assessment of heart rate variability (high-frequency component detected by nonspectral or spectral analysis) and baroreceptor sensitivity.

## 6.3 Vasospastic Angina

The incidence of vasospastic angina is higher in Japan than in Western countries. The risk of sudden death is particularly high in patients with multivessel spasm, so a diagnosis is important. Vasospastic angina frequently occurs at night or early in the morning, and detection of ischemic changes on ECG at the time of attack is important for making a diagnosis. Therefore, Holter ECG should be performed for 24–48 hours as the first test.[63] However, it is often difficult to detect ischemic changes during attacks in the real clinical setting. A cold stimulation test performed in the early morning can be useful for a diagnosis of vasospastic angina, as well as a hyperventilation test or exercise test. Imaging of myocardial sympathetic nerves (I-123-MIBG) or myocardial fatty acid metabolism (I-123 BMIPP) may identify regions of ischemia if severe myocardial ischemia occurs during attacks.[426,1235]

A coronary spasm provocation test by coronary angiography using acetylcholine or ergonovine provides direct visual confirmation of coronary spasm. To improve diagnostic accuracy, it is recommended that calcium-channel blockers and long-acting nitrates should be withdrawn for at least 48 hours, if possible. The criterion for a positive coronary spasm provocation test is transient total/subtotal occlusion (>90% stenosis) of a coronary artery associated with signs of myocardial ischemia (anginal pain and ischemic ST changes).[63] In patients with variant angina, the sensitivity and specificity of provocation testing with acetylcholine are high, being 89–93% and 100%, respectively. Because smoking and drinking are important risk factors for vasospasm, guidance about lifestyle modification is essential, such as cessation of smoking and reduction of alcohol consumption or abstinence from alcohol.

## 6.4 Asymptomatic Myocardial Ischemia

Asymptomatic myocardial ischemia is defined by objective evidence of myocardial ischemia in the absence of symptoms

suggesting angina, such as chest pain. In general, the classification of Cohn et al is used.[71] Type I is asymptomatic myocardial ischemia without signs of myocardial infarction or angina pectoris, type II is asymptomatic myocardial ischemia occurring after myocardial infarction, and type III is asymptomatic myocardial ischemia accompanied by angina pectoris. Elderly patients, patients with diabetes mellitus, and patients with a history of myocardial infarction or revascularization are more likely to develop asymptomatic myocardial ischemia. A study using myocardial perfusion SPECT detected myocardial ischemia in 27% of asymptomatic patients without known cardiac disease.[1236] Treatment of asymptomatic myocardial ischemia is similar to that of symptomatic ischemia; however, there are cases of improvement of QOL not being obtained after revascularization because the patient was asymptomatic. As with symptomatic myocardial ischemia, it is important to fully investigate the range and extent of myocardial ischemia using various tests and select the treatment strategy with the aim of improving QOL and the prognosis.

### 6.5 Future Challenges

Large-scale prospective studies on the investigation and treatment of coronary heart disease have recently been conducted in Japan, yielding clinical data on Japanese patients. Because there are racial differences in the pathology of coronary heart disease, it is desirable to accumulate more clinical data from Japanese patients in the future, in order to formulate treatment strategies based on the findings. Detection of vulnerable plaques at sites other than the culprit lesion is important for preventing ACS. Plaque instability does not always correlate with coronary artery stenosis, so tests for myocardial ischemia cannot detect vulnerable plaques. In the future, noninvasive modalities such as CCTA and MRA may be used for assessment of plaque characteristics.

Recommendations and levels of evidence for testing methods of selecting the treatment strategy are shown in **Table 57**.

## 7. Evaluating the Effect of Treatment

The aim of treating chronic stable coronary heart disease is to improve symptoms and the long-term prognosis. Various stress tests are used to assess the alleviation of myocardial ischemia or improvement of the threshold for induction of ischemia after treatment. Exercise tolerance is an objective predictor of the prognosis, and it was reported that the survival rate improves by 12% for each 1 Met increase in exercise tolerance. To assess the influence of treatment on the prognosis, improvement of prognostic factors is investigated. There are several clinical categories of coronary heart disease, and the tests used to assess the response to treatment vary among these categories. In this section, coronary heart disease is divided into 4 clinical categories: coronary heart disease without myocardial infarction, OMI, vasospastic angina, and asymptomatic myocardial ischemia. The role of various tests in evaluating the effect of treatment is described for each heart disease category.

### 7.1 Coronary Heart Disease Without Myocardial Infarction

#### 7.1.1 ECG, Exercise ECG, Cardiac Radionuclide Imaging, and Stress Echocardiography

When evaluating the effect of treatment for coronary heart disease, confirming the improvement of symptoms and alleviation of myocardial ischemia are important. Successful treatment of ischemic heart disease, whether invasive or noninvasive, results in an increase in exercise tolerance.[1237,1238] Stress echocardiography can assess the therapeutic effect on myocardial ischemia by confirming that wall motion abnormalities that existed before treatment are no longer detected. Exercise ECG is useful because it can simultaneously evaluate improvement of myocardial ischemia and exercise tolerance.

In patients who have coronary heart disease without myocardial infarction, assessment of myocardial hypoperfusion by exercise myocardial perfusion imaging is useful. However, because myocardial blood flow images obtained during exercise reflect the relative blood flow distribution, detection of coronary artery lesions may be difficult in patients with triple-vessel disease.[1239] TI-201 myocardial perfusion imaging is widely used for a diagnosis of ischemia, regional localization, assessment of severity, and prediction of the prognosis. Assessment of myocardial perfusion with Tc-99 m-labeled agents has the same diagnostic value as TI-201 imaging, with the advantage of allowing simultaneous assessment of blood flow and wall motion by ECG-gated acquisition.

Imaging of myocardial fatty acid metabolism with I-123 BMIPP and imaging of myocardial sympathetic nerves with I-123-MIBG allow assessment of myocardial ischemia without stress loading by comparison with myocardial blood flow images obtained at rest. This approach is particularly useful in the elderly and in patients who cannot tolerate exercise.[445,1223] However, defects on I-123 BMIPP and I-123-MIBG images may potentially represent "ischemic memory", reflecting myocardial ischemia that existed for several weeks prior to testing. Therefore, it is necessary to distinguish pretreatment "ischemic memory" from the effects of transient ischemia during treatment when these imaging modalities are used immediately after treatment. When I-123-MIBG myocardial sympathetic nerve imaging is performed, autonomic nervous system dysfunction in patients with diabetes mellitus or elderly patients often leads to decreased inferior wall accumulation even if myocardial blood flow is normal. Hence, care is required when evaluating the response to treatment by this imaging method.

Myocardial perfusion PET using N-13 ammonia or Rb-82 allows measurement of the CFR during perfusion imaging and is useful for determining the effect of drug therapy.[471] In addition, imaging of myocardial glucose metabolism with $^{18}$F-FDG is useful for evaluation of myocardial viability.[1067,1240]

#### 7.1.2 CT, MRA, Coronary Angiography, FFR, and FFR-CT

Investigation of the coronary arteries is required in patients with anginal symptoms or suspected myocardial ischemia. Evaluation of coronary artery stenosis and the collateral circulation by coronary angiography is essential to determine the strategy for invasive treatment. Recent advances in CT have led to a rapid increase in its use for noninvasive imaging of the coronary arteries. CT has the advantage

that noninvasive assessment of the coronary arteries can be performed in patients who cannot undergo exercise testing with an adequate load or in whom ischemia cannot be ruled out, and it is also used to characterize the coronary artery wall.[541,1241] Because of the requirement for ECG gating, it is difficult to perform CCTA in patients with tachycardia or arrhythmia. Coronary MRA has the advantages of avoiding radiation exposure and no requirement for contrast medium. Another advantage is that coronary artery calcification only has a small influence on images, but the technician needs to be experienced and skilled. Coronary angiography is an invasive procedure, which is appropriate when there is a strong suspicion of myocardial ischemia and the treatment strategy needs to be decided. Determining the FFR during coronary angiography is useful for evaluating myocardial ischemia. In general, revascularization is indicated if the FFR is <0.75, while an FFR of 0.75–0.80 is considered to be borderline.[315,560,579,582,1242]

On the other hand, there is limited evidence that the FFR is useful for evaluating the effect of treatment. In patients with implantation of bare metal stents, a significantly higher incidence of MACE was reported in the case of FFR <0.90 immediately after PCI.[1243] Medium- to long-term prognostic studies have shown that the incidence of MACE was significantly lower when FFR ≤0.86 and target vessel failure was significantly less frequent in patients whose FFR was ≤0.85 or ≤0.88.[1213,1244] However, there are still many issues without consensus, such as whether an FFR cutoff value should be set for use immediately after PCI, whether additional PCI should be performed if the FFR is low, and whether the FFR should be tested immediately after PCI. FFR-CT has recently attracted attention and is suggested to be useful for evaluation of de novo lesions, but is not indicated for severely calcified lesions or stented lesions. According to the Japanese Circulation Society Guideline for Appropriate Use of FFR-CT,[591] the diagnostic performance of FFR-CT for functional ischemia is not completely consistent with that of FFR, and further evidence is needed to clarify whether FFR-CT has equivalent diagnostic and prognostic value to FFR.

## 7.2 Old Myocardial Infarction

### 7.2.1 Angina Pectoris or Myocardial Ischemia Associated With OMI

#### a. Symptoms and ECG

When OMI is complicated by effort angina, it is important to assess the patient's symptoms in order to evaluate the effect of treatment. Exercise ECG and stress myocardial perfusion imaging can be used to determine the effect on exertional myocardial ischemia. The Japanese Society of Electrocardiology has issued the Antianginal Drug Evaluation Subcommittee Report on exercise ECG.[1245] The Society used improvement of ST depression at the same exercise time and improvement of exercise duration as the indices for judgment. In patients with OMI and abnormal Q waves, ST elevation on ECG during exercise loading may indicate myocardial ischemia or left ventricular asynergy. Although there are morphological differences in the elevated ST segments, it is not always easy to distinguish these conditions solely from the ECG findings.[1246]

Asymptomatic myocardial ischemia is not uncommon in OMI. The incidence of fatal myocardial infarction, heart failure, and overall mortality is comparable in patients with asymptomatic myocardial ischemia or symptomatic disease, which means that it is important to investigate the response to treatment.[1162,1247] In patients with asymptomatic myocardial ischemia, Holter ECG and stress myocardial perfusion imaging are also used in addition to exercise ECG. The frequency of ST depression over 24 hours and the total duration of ST depression are used as indices for Holter ECG.

#### b. Stress Myocardial Perfusion Imaging

With stress myocardial perfusion imaging, the effect on myocardial ischemia can be comprehensively assessed from the presence and extent of transient perfusion defects, in addition to symptoms during stress loading and the ECG information. Many patients with myocardial infarction have hypoperfusion even at rest, and improvement of transient hypoperfusion during stress testing serves as an index for assessing the effect of treatment.[1248] This applies to both infarcted and noninfarcted myocardium. With Tl-201 myocardial scintigraphy, both the size of the transient perfusion defect and the rate of tracer uptake in the hypoperfused area (% uptake) are investigated.[1249]

Tc-99 m is superior to TI-201 for ECG-gated testing. The presence of a transient defect on stress myocardial perfusion imaging after revascularization generally indicates restenosis or graft occlusion. Even if ST depression is revealed by stress ECG in the period immediately after revascularization, myocardial perfusion imaging may still be normal. Moreover, transient defects can be seen on stress myocardial perfusion imaging even when the target vessel is patent. Such false-positive findings are common when arterial grafts are used for CABG.[1073] Thus, caution should be exercised when assessing restenosis after PCI or CABG. Higher sensitivity and specificity for restenosis can be obtained by performing stress myocardial perfusion imaging at 4–6 weeks after revascularization.

### 7.2.2 Left Ventricular Dysfunction With Myocardial Ischemia (Ischemic Cardiomyopathy)

#### a. Left Ventricular Systolic and Diastolic Function

Both multivessel disease and left ventricular dysfunction are independent indicators of a poor prognosis, so their combination results in a particularly poor prognosis. In these patients, the goal of treatment is to achieve improvement of myocardial ischemia and left ventricular function. The effect of treatment on myocardial ischemia is evaluated by the methods mentioned above.

In patients with left ventricular dysfunction due to myocardial ischemia, revascularization is aimed at improving cardiac function and reducing events. LVEF, an index of contractility, is often used to investigate improvement of cardiac function and is frequently measured by echocardiography. On the other hand, myocardial scintigraphy using ECG-gated SPECT and cardiac MRI can simultaneously evaluate left ventricular function and myocardial perfusion, so these methods are useful for assessing the response to treatment in patients with ischemic cardiomyopathy.

#### b. Mitral Regurgitation

Mitral regurgitation may occur in patients who have left ventricular dysfunction associated with myocardial infarction, and the prognosis is poor. Mitral regurgitation associated with chronic coronary heart disease is generally caused by functional mitral incompetence due to enlargement of the mitral annulus and papillary muscle dysfunction secondary to left ventricular remodeling. Because such

functional incompetence strongly correlates with the survival rate and incidence of heart failure, optimum medical treatment in accordance with the guidelines is essential.[135,1250,1251] In addition, surgical treatment should be considered in patients with symptomatic mitral regurgitation. To assess the response to treatment, detection of mitral regurgitation and evaluation of its severity are performed by color Doppler imaging. In the case of assessment by transthoracic echocardiography being difficult to perform, transesophageal echocardiography may be performed instead.

#### 7.2.3 Prevention and Treatment of Postinfarction Left Ventricular Remodeling

In some patients, myocardial scarring progresses to fibrosis after myocardial infarction, and then the left ventricle expands due to mural thinning in the infarct zone. Hypertrophy of cardiomyocytes in the noninfarcted areas and interstitial fibrosis also occur, resulting in impairment of left ventricular systolic and diastolic function. This process is called chronic postinfarction left ventricular remodeling and indicates a poor prognosis.[1252,1253]

Acute left ventricular remodeling occurs from several weeks to months after myocardial infarction. However, left ventricular remodeling is a prolonged process in patients with chronic infarction, and it is therefore important to assess changes in left ventricular end-diastolic volume over time. At the same time, ESV, LVEF, left ventricular cardiac mass, left ventricular wall thickness, and myocardial viability should also be evaluated. Methods of assessing the response to treatment include echocardiography, ECG-gated myocardial SPECT, and cardiac MRI. Although echocardiography is simple and can be repeated easily, there are problems with inadequate spatial and temporal resolution. Cardiac MRI has the advantage of excellent spatial resolution and can measure the left ventricular volume and LVEF without radiation exposure. In addition, myocardial necrosis and fibrosis can be investigated by assessing LGE (Class IIa, Level B evidence).

### 7.3 Vasospastic Angina

Evaluation of the effect of treatment for vasospastic angina differs from that for stable effort angina, because the pathogenesis differs and there are differences in pathology and clinical features between the diseases. However, alleviation of chest pain and improvement of the prognosis are common treatment goals for both diseases. Chest pain is commonly assessed to evaluate the response to treatment, and judgment is based on the frequency of attacks and the dosage of sublingual nitroglycerin. In patients who have angina pectoris associated with coronary spasm, the frequency of chest pain varies and there is a risk of serious complications. Hence, observation should not be unduly prolonged and treatment should be initiated or intensified as soon as symptoms indicate an inadequate response.

Objective tests, such as Holter ECG or event-triggered Holter ECG, can also be used to investigate improvement of ischemic attacks at rest. Holter ECG allows analysis of the frequency of ST elevation, the duration of ST elevation, and the maximum extent of ST elevation. Accordingly, the effect of treatment can be determined from the ECG findings regardless of the presence/absence of chest pain. Patients with mild coronary spasm who do not have complete coronary artery occlusion by spasm may show ST depression at the time of attacks. Even if coronary spasm causes complete occlusion of the affected vessel, myocardial ischemia may remain endocardial and not become transmural due to development of collateral circulation, resulting in ST depression. Among the diagnostic imaging tests, myocardial I-123 BMIPP and I-123-MIBG imaging both have a high sensitivity and specificity for vasospastic angina and can be used to assess the response to treatment or to decide on the initiation or intensification of drug therapy.[426,428,1254–1256]

It has also been pointed out that vasospastic angina can show spontaneous remission, and it is important to determine the differences between patients who need to continue drug therapy and those who can reduce or cease it.[1257] However, it is difficult to assess the long-term effect of treatment for vasospastic angina, and discontinuation of drug therapy may lead to the onset of further attacks or sudden death. Therefore, caution should be exercised when reducing, suspending, or discontinuing drugs, even in patients with apparent spontaneous remission. The most important prognostic factor for vasospastic angina is a history of out-of-hospital cardiac arrest, followed by smoking, rest angina, significant organic stenosis, multivessel spasm, ST elevation during attacks, and use of $\beta$-blockers, and special attention should be paid to patients with these factors. Guidance to quit smoking is also important in patients with vasospastic angina.[664]

Regarding the long-term prognosis of vasospastic angina, the 3-year survival rate was reported to be at least 96% in Japan.[945,1258,1259] It was reported that progression to myocardial infarction is most likely to occur within a few months after the onset of vasospastic angina.[1257] Subsequently, the incidence of acute myocardial infarction is low and the clinical course is usually good, but it should be noted that sudden death may occur in some patients.

### 7.4 Asymptomatic Myocardial Ischemia

#### 7.4.1 Selection of Treatment

Asymptomatic myocardial ischemia is a condition in which transient myocardial ischemia is detected by various tests in the absence of anginal pain, and the Cohn classification is often used in the clinical setting.[1002] Although there is insufficient evidence to advocate periodic testing for the presence of asymptomatic myocardial ischemia, it is desirable to assess the response to treatment when a patient develops comorbidities or when progression of risk factors is suspected.

#### 7.4.2 Indices for Evaluation of Treatment

The main evaluation methods used in patients with asymptomatic myocardial ischemia are stress ECG, Holter ECG, stress echocardiography, and stress myocardial perfusion imaging. Patients with diabetes mellitus often have asymptomatic myocardial ischemia and myocardial infarction shows a worse prognosis when it is associated with diabetes mellitus. In patients with both angina pectoris and asymptomatic myocardial ischemia (Cohn type III), disappearance of symptoms should not be regarded as the only index for assessing the response to treatment. Tests for determining the effect of treatment on asymptomatic myocardial ischemia are described below. It should be noted that the tests selected will largely depend on the availability of equipment and skilled technicians.

#### 7.4.3 Exercise ECG

Exercise ECG is the most frequent modality for assessing

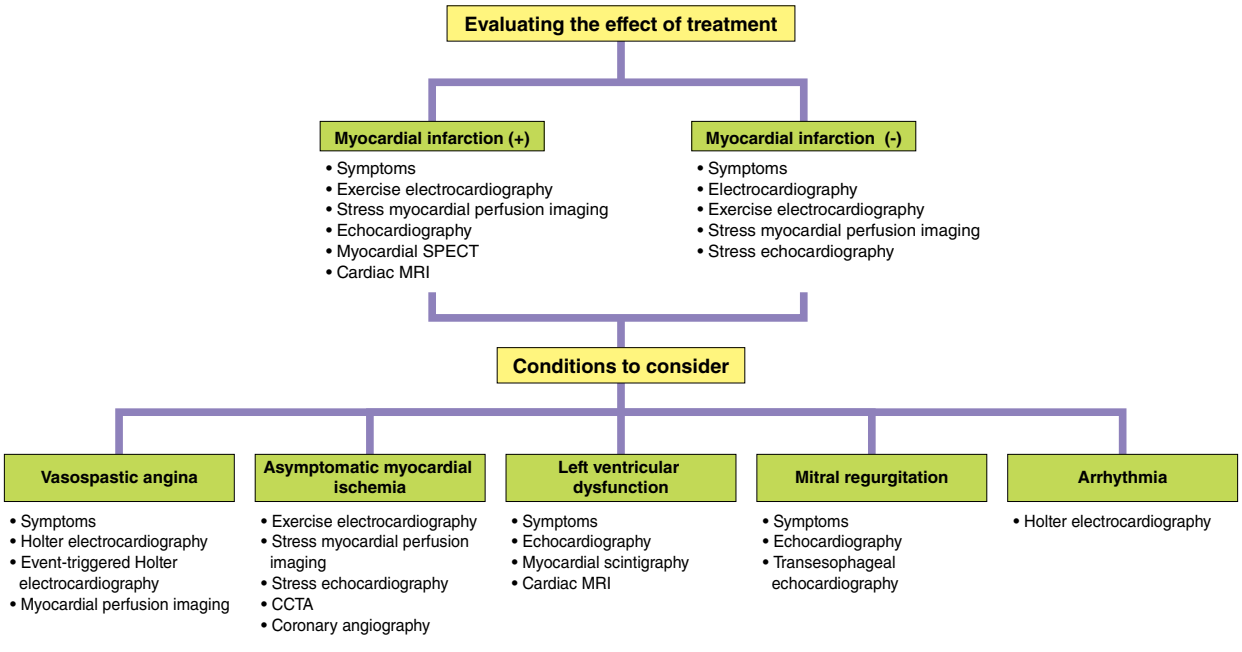



**Figure 25.** Algorithm for evaluation of treatment efficacy.

both the short-term and long-term effects of treatment. Cohn types II and III asymptomatic patients with positive exercise ECG are considered to be clinically equivalent to symptomatic patients with positive exercise ECG. If exercise ECG is negative or exercise tolerance is maintained, the prognosis is good and this serves as a guide for assessing the effect of treatment.[1260] The disadvantages of this method include it being limited to patients who can perform exercise, sufficient exercise loading is necessary, the ECG waveform needs to be determinable, and sensitivity is low.

### 7.4.4 Stress Myocardial Perfusion Imaging

Stress myocardial perfusion imaging can comprehensively evaluate the effect of treatment for myocardial ischemia based on the presence/absence and extent of transient perfusion defects, in addition to symptoms at the time of stress loading and ECG information. Accordingly, detection rate for ischemia is higher with stress myocardial perfusion imaging than with exercise ECG or stress echocardiography. Patients with restenosis after PCI are often asymptomatic, but a transient defect on stress myocardial perfusion imaging generally suggests restenosis or occlusion.[1261] This test is also useful in patients with asymptomatic occlusion of bypass grafts after CABG, particularly vein grafts.[1073]

Because reperfusion of nonviable myocardium does not improve the prognosis, evaluation of myocardial viability by stress myocardial perfusion imaging is also useful for deciding the treatment strategy. The incidence of cardiac events in patients with normal findings on stress myocardial perfusion imaging is approximately 0.6% per year in Japan and other countries, indicating that this method is also useful for predicting the prognosis.[223,1189,1262–1265]

### 7.4.5 Stress Echocardiography

After the onset of ischemia, wall motion decreases before symptoms or ECG abnormalities develop. Hence, stress echocardiography is useful for detecting ischemic events at the earliest possible timing. Even in patients with a positive result of treadmill exercise ECG, the incidence of cardiac events is low if wall motion abnormalities are not detected by stress echocardiography. In contrast, the probability of cardiac events is high in patients with wall motion abnormalities on stress echocardiography.[157,1266] Disadvantages of stress echocardiography are that determination of wall motion abnormalities is semiquantitative, and accurate evaluation depends on the experience and skill of the evaluator.

### 7.4.6 CCTA

CCTA has recently been used extensively in patients with asymptomatic ST changes and suspected ischemia. If adequate CT images can be obtained, for example by regulating the heart rate with a $\beta$-blocker, it is possible to determine the coronary artery diameter and assess plaques. Because of its high specificity, CCTA is a powerful tool for demonstrating the absence of coronary lesions.[1267,1268] It is also effective for detecting stenosis, but is not so useful for evaluation of calcified lesions, and the requirement for contrast medium and radiation exposure is unavoidable.

### 7.4.7 Coronary Angiography

Coronary angiography is the most appropriate test for evaluating the anatomical features of the coronary arteries. However, clinical and functional indices have recently been considered more important than morphological indices in patients with chronic coronary heart disease, and there have been many reports that coronary angiography is unnecessary unless there are significant ischemic changes on exercise ECG or myocardial perfusion imaging, etc.[647,1269–1271] Moreover, the clinical significance of angiography in this setting has not been established, including its cost and effectiveness.

**Table 58. Recommendations and Levels of Evidence for Testing Methods to Assess Ischemia Treatment**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **Exercise ECG** | | | | |
| When ischemia is suspected, a readable electrocardiogram can be obtained, and when there are no physical restrictions | I | A | A | I |
| **Stress echocardiography** | | | | |
| When a skilled evaluator is available | IIa | A | B | I |
| **CCTA** | | | | |
| If assessment of ischemia is difficult using exercise stress or ECG | I | A | A | I |
| **Holter ECG** | | | | |
| Vasospastic angina | IIa | C | B | IVa |
| **Echocardiography** | | | | |
| Evaluation of left heart function and regional wall motion in patients with cardiac dysfunction, after myocardial infarction, or valvular disease | I | B | B | III |
| **Cardiac MRI** | | | | |
| Evaluation of left heart function and regional wall motion in patients with myocardial infarction, cardiac dysfunction, or valvular disease | IIa | C | B | IVa |
| Evaluation of the effect of treatment for myocardial ischemia | IIb | C | C1 | II |
| **Coronary MRA** | | | | |
| Anatomical evaluation of the coronary arteries | I | A | B | I |
| **Radionuclide imaging** | | | | |
| Evaluation of left heart function in patients with heart failure | IIa | B | B | IVa |
| Vasospastic angina | IIb | C | B | IVa |
| Evaluation of the effect of treatment for myocardial ischemia | IIa | C | B | IVa |
| **Stress myocardial perfusion imaging** | | | | |
| Evaluation of the effect of ischemia therapy in patients who cannot perform exercise | I | B | B | I |
| **Coronary angiography** | | | | |
| Routine evaluation of patients | III | B | D | II |

CCTA, coronary computed tomography angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

## 7.5 Arrhythmia

Myocardial infarction and myocardial ischemia are responsible for the development of various arrhythmias, including ventricular arrhythmias.[70] If myocardial ischemia persists after treatment, it may lead to heart failure and sudden cardiac death, making alleviation of ischemia very important. Arrhythmias may be transient in the acute phase of ACS and do not necessarily require ongoing treatment, but OMI patients often have a substrate for ventricular arrhythmia. Therefore, care should be exercised if sustained ventricular tachycardia and/or ventricular fibrillation occur from 48 hours after the onset of myocardial infarction. In addition to symptoms, cardiac function and the presence/absence of ventricular tachycardia are important indicators for evaluating the effect of treatment and deciding the indications for ICD implantation.

A high incidence of atrial fibrillation (AF) has been reported in patients with coronary heart disease, particularly myocardial infarction. Tachycardia and arrhythmia due to AF give rise to worsening of cardiac function and coronary blood flow after myocardial infarction. The incidence of AF after myocardial infarction was reported to be 6–13%, with the risk factors being advanced age, heart failure, diabetes mellitus, etc.[1272–1274] There have been many reports about the association between AF and ventricular tachycardia or death. Patients with myocardial infarction complicated by AF have a poor short-term and long-term prognosis.[1274–1277]

The ESC Guideline for Management of Patients with Stable Coronary Heart Disease does not recommend Holter monitoring or arrhythmia provocation testing to detect arrhythmias in asymptomatic patients with chronic ischemic heart disease.[125] However, arrhythmias may occur frequently in the early stage of myocardial ischemia and may be a risk factor for sudden death, heart failure, etc. It is also known that the mortality rate is high in patients with heart failure complicated by arrhythmia and patients with cardiac dysfunction. It is therefore worthwhile to test these patients even if they are asymptomatic.

## 7.6 Future Challenges

The algorithm for evaluation of the effect of treatment is

summarized in **Figure 25**. As a result of treatment, there has been a remarkable improvement in the quality of methods for assessing the response to treatment. Nevertheless, in the era of extensive coronary catheter intervention, these diagnostic tests are overused in Japan. There are limited cost–benefit analyses to justify the use of these modalities and selecting strategies that are clinically and economically appropriate remains a major issue. Recommendations and levels of evidence for selecting treatment strategies and assessing myocardial ischemia are shown in **Tables 57** and **58**, respectively.

## 8. Diagnosis and Assessment in Children at High Risk for Coronary Heart Disease Including Kawasaki Disease

### 8.1 Target Diseases

Kawasaki disease is the main characteristic cause of chronic coronary heart disease in children. Other causes include congenital coronary artery anomalies, congenital heart disease, malformation syndrome, inborn errors of metabolism, and cardiac allograft vasculopathy. Many patients with these diseases have achieved long-term survival after receiving treatment during childhood. However, even if asymptomatic during childhood, coronary heart disease may develop in adulthood. Accordingly, ongoing management by a physician for adults is important. Coronary heart disease accounts for 24–31% of sudden deaths in children and young adults.[1278,1279] The current school heart examination has limited value for detection of coronary disease, and caution should be required if chest pain or syncope occurs during exercise.

**Table 59. Classification of Congenital Coronary Artery Malformations**

| |
|---|
| **1. Abnormalities of the coronary artery origin and course** |
| 1.1 Origin from the aortic root |
| 1.1.1 Single coronary artery |
| 1.1.2 Abnormal origin close to the normal origin: high take-off, low take-off, and commissural ostium |
| 1.1.3 Anomalous aortic origin of a coronary artery |
| a. Anomalous aortic origin of the left main coronary artery |
| b. Anomalous aortic origin of the right coronary artery |
| c. Anomalous aortic origin of a coronary artery from the noncoronary sinus |
| d. Other anomalies |
| 1.2 Origin from sites other than the aortic root |
| 1.2.1 Pulmonary artery |
| a. Anomalous left coronary artery arising from the pulmonary artery (Bland-White-Garland syndrome) |
| b. Anomalous right coronary artery arising from the pulmonary artery |
| c. Anomalous left anterior descending coronary artery arising from the pulmonary artery sinus |
| d. Anomalous left circumflex coronary artery arising from the pulmonary artery |
| e. Total anomalous origin of the coronary arteries from the pulmonary artery |
| 1.2.2 Aortic arch and branches |
| **2. Coronary artery ostial stenosis/atresia** |
| 2.1 Coronary artery ostial stenosis |
| 2.2 Coronary artery ostial atresia |
| **3. Anomalous coronary artery course** |
| 3.1 Myocardial bridge |
| 3.2 Coronary artery duplication |
| 3.3 Others: absent or hypoplastic coronary artery, subendocardial coronary artery, etc. |
| **4. Anomalies of coronary artery termination** |
| 4.1 Coronary artery fistula |
| 4.2 Coronary sinus anomalies: ostial atresia, absence/hypoplasia |

(Reproduced from Angelini et al 2002,[1287] with permission.)

#### 8.1.1 Kawasaki Disease

Kawasaki disease (KD) is a vasculitic syndrome that usually occurs in infants and children aged 4 years or younger, and 2–3% of patients develop coronary artery aneurysms even if acute treatment is provided.[1280] According to the Japanese nationwide survey,[1281] the number of cases and incidence rate of KD continued to increase until 2015 and showed a slight decrease in 2016, with the annual number of cases being approximately 15,000. The prognosis of patients with coronary artery aneurysms is related to the internal diameter of the aneurysm. In patients with a measured aneurysm diameter ≤4 mm, there is little or no increase in IMT and stenotic lesions are rare.[1282]

On the other hand, aneurysms ≥6 mm in diameter (especially in young children with a body surface area <0.5 $m^2$) are associated with a high risk of coronary artery stenosis.[1283,1284] According to a recent study based on the z score, giant aneurysms with a z score ≥10 or actually measured at ≥8 mm had a worse prognosis (regression rate: 19%; incidence of coronary events: 34%; incidence of major cardiac events: 18–23%) than aneurysms with a z score <5 (regression rate: 87%; incidence of coronary events: 0%; incidence of major cardiac events: 0%).[1285,1286]

#### 8.1.2 Coronary Artery Anomalies

Congenital coronary artery anomalies occur in approximately 1% of the general population and can be divided into anomalies of the origin/course, ostial stenosis/occlusion, anomalies of intrinsic coronary artery anatomy, and anomalous termination (**Table 59**).[1287] Coronary artery anomalies are often associated with congenital heart disease, but may occur in apparently healthy children and can cause sudden death during exercise.[1278,1279] In particular, the risk is high when the left coronary artery arises from the right coronary sinus and runs between the 2 great vessels, and this anomaly accounts for approximately one-third of sudden cardiogenic deaths in young adults.[1278]

#### 8.1.3 Congenital Heart Disease

Coronary artery anomalies are commonly associated with anomalies of the great vessels and aortic valve, including complete transposition of great arteries, double outlet right ventricle, tetralogy of Fallot, and truncus arteriosus. Preoperative assessment of coronary artery anomalies should not be omitted, because it affects the procedure for cardiac surgery. Careful monitoring for coronary heart disease should be performed after coronary artery transplantation such as the Jatene procedure or the Ross procedure. Coronary artery stenosis/occlusion was reported in 4–17% of patients undergoing the Jatene procedure,[1288] occurring in 40% and 7% of patients with or without signs of coronary heart disease, respectively.[1289]

#### 8.1.4 Malformation Syndrome and Inborn Error of Metabolism

Coronary artery anomalies may be seen in 22q11.2 deletion syndrome accompanied by great vessel anomalies and in Williams syndrome accompanied by supravalvular aortic stenosis. Williams syndrome is associated with a high incidence of coronary ostial stenosis (5–19%), as well as extensive stenosis, occlusion, or enlargement of the coronary arteries.[1290] Inborn errors of metabolism, such as familial hyperlipidemia and infantile systemic arterial calcification, cause children to have a similar risk of coronary heart disease as adults. In particular, improvement in the accuracy of genetic testing has shown that FH is more frequently associated with coronary heart disease than was realized hitherto.[888]

### 8.2 Electrocardiography

#### 8.2.1 Exercise ECG

Exercise ECG is of great clinical significance because it is simple and relatively safe to perform in children. If resting ECG clearly suggests myocardial ischemia, whether stress testing should be performed needs to be carefully considered. Stress testing is high risk in patients with pulmonary hypertension, dilated and restrictive cardiomyopathy, hypertrophic cardiomyopathy accompanied by moderate left ventricular outflow tract stenosis (contraindicated for severe cases), and exercise-related syncope of unknown cause.[1291]

The Master 2-step test is a simple exercise loading method, but the double Master (3 min; commonly used in adults) may not be sufficient in children with a high exercise tolerance. In infants aged 3 years or older, the jump test, in which children jump at a given tempo, may also be used.[1292] Treadmill and ergometer tests can generally be performed in school-aged children. Use of a bicycle ergometer (which children ride at their own tempo) imposes less stress, but is safer. For detection of myocardial ischemia in patients with KD and coronary artery aneurysms, exercise stress ECG only has a sensitivity of 33–46%,[1293,1294] and it is therefore better to combine exercise tests with diagnostic imaging as appropriate.[1295]

#### 8.2.2 Resting ECG, Holter ECG, etc.

Resting ECG and Holter ECG can even be performed in infants who cannot exercise. Attention should be paid to ST-T changes and abnormal Q waves. QT dispersion is reported to be high in patients with coronary lesions caused by KD.[1280] Extended ECG, including Holter monitoring, may be useful in the diagnosis of syncope, chest pain, or arrhythmias caused by myocardial ischemia. Although body surface ECG, SAE, and magnetocardiography have also been studied in children, these methods are not widely used in daily practice.

### 8.3 Echocardiography

#### 8.3.1 Resting Echocardiography

The noninvasiveness and rapidity of resting transthoracic echocardiography (TTE) are advantages for use in children. The coronary arteries of children can be easily visualized by TTE. Therefore, careful observation of malformations, including the origin and course, and measurement of the internal diameter, should be carried out. Echocardiography is also useful for assessing structural abnormalities of the heart, valvular disease, thrombosis, and systolic/diastolic function, but it has limitations for detecting myocardial ischemia.

For diagnosis of coronary artery dilatation/aneurysm, the normal internal coronary artery diameter has been defined <3 mm under the age of 5 years and <4 mm at age 5 or older in accordance with the literature on KD[1286,1296] (there are some reports in which it was ≤3 mm and ≤4 mm, respectively,[1297] but the source of data for children aged 5 years or older was unclear). According to a statement issued by the AHA in 2017 on the Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease,[1295] a z score <2.0 is defined as normal. Given that the normal value to calculate the z score has been established in Japanese children too, the z score is expected to be used more widely in the future.[1296]

According to the classification in the Japanese guidelines,[1280] an internal coronary artery diameter ≤4 mm is considered to represent dilation (or a small aneurysm), 4–8 mm is a medium-sized aneurysm, and ≥8 mm is a giant aneurysm, with the same management as for giant aneurysms being recommended in the case of diameter ≥6 mm. In another classification, dilation is defined as less than 1.5-fold of the peripheral coronary diameter, 1.5–4-fold is a medium aneurysm, and >4-fold is a giant aneurysm in children aged 5 years or older, and such classification is a type of body size-based correction. According to the AHA guidelines,[1295] a z score of 2 to <2.5 (or a decrease of at least 1 during follow-up if initially <2) indicates dilation, from 2.5 to <5 indicates a small aneurysm, from 5 to <10 with the actual measured value <8 mm indicates a medium aneurysm, and ≥10 or the actual measured value ≥8 mm indicates a giant aneurysm.

#### 8.3.2 Stress Echocardiography, etc.

In children, cardiac function and hemodynamics, including myocardial ischemia, are assessed by echocardiography with exercise or pharmacological stress.[1298] Dobutamine stress echocardiography can detect ischemic lesions in patients with KD and patients who have undergone the Jatene procedure for complete transposition of the great arteries.[1299,1300] It is useful for predicting the long-term risk of major cardiac events in patients with KD.[1301] There have also been reports about using myocardial contrast echocardiography and 3-dimensional echocardiography for KD.[1280]

### 8.4 Myocardial Perfusion Imaging

#### 8.4.1 Target Diseases

##### a. Kawasaki Disease

In children, myocardial perfusion imaging is often used to investigate coronary artery lesions caused by KD.[1302,1303] With regard to diagnostic imaging for follow-up of coronary artery lesions due to KD, an AHA statement recommends selecting the methods and testing intervals according to the internal diameter of the coronary artery aneurysms.[1280,1295] For patients with small or larger coronary artery aneurysms (z score ≥2.5), including medium and giant aneurysms, stress echocardiography, stress MRI, stress myocardial perfusion SPECT, and PET receive a Class IIa recommendation with evidence level B, and are designated as "reasonable" ischemia-inducing tests. It is stated that confirmation of the presence/absence of ischemia by stress testing is the most important objective of the examination. Stress myocardial perfusion SPECT is recom-

mended every 2–3 years for small coronary artery aneurysms, every 1–3 years for medium aneurysms, and every 6–12 months for giant aneurysms.

#### b. Coronary Artery Anomalies

In patients with coronary artery anomalies, myocardial perfusion imaging is sometimes used for preoperative assessment of anomalous origin of the left coronary artery from the pulmonary artery.[1304] Mismatch of myocardial blood flow and fatty acid metabolism, as well as improvement of myocardial blood flow in the early postoperative period, have been reported.[1305]

#### c. Congenital Heart Disease

The target patients are those who have received coronary artery transplantation by the Ross or Jatene procedure. In a study of 10 children aged ≤6 years who underwent the Jatene procedure for complete transposition of great arteries, no abnormalities were found by resting or adenosine stress myocardial perfusion SPECT.[1306] On the other hand, it was reported that coronary artery stenosis and occlusion occurred in 11.3% of patients after the Jatene procedure, and that myocardial perfusion SPECT showed no abnormalities in some patients despite the presence of left coronary artery ostial stenosis and ventricular fibrillation during follow-up.[1307]

### 8.4.2 Radiopharmaceuticals

The consensus guidelines for nuclear medicine studies in children recommend Tc myocardial perfusion agents (Tc-99 m sestamibi and Tc-99 m tetrofosmin) as standard pediatric agents in consideration of reducing radiation exposure.[1308] Thallium chloride, such as Tl-201, is not recommended for children because the exposure dose in the myocardial perfusion stress/rest protocol is expected to be approximately 8–10-fold greater than that of Tc preparations.[1302]

### 8.4.3 Radiation Exposure

In the USA, 42.5% of children younger than 18 years have undergone radiography and 0.7% have undergone nuclear medicine studies,[1309] indicating that nuclear studies are not widely performed on children. In Japan, nuclear medicine studies performed in children aged 15 years or younger account for 3.4% of all nuclear medicine studies, and cardiac radionuclide imaging accounts for 2.5% of all nuclear medicine studies in children, so both percentages are quite low.[1310] However, children often require repeated examinations from infancy, especially those with coronary heart disease after KD, and cardiac radionuclide imaging from childhood could result in major cumulative exposure to radiation. A study of radiation exposure among adults in the USA found that overall medical radiation exposure increased from an effective dose of 0.54 mSv (1980–1982) to 3.0 mSv (2006), while radiation exposure from nuclear medicine studies increased from 0.14 mSv (1980–1982) to 0.77 mSv (2006), indicating that nuclear studies accounted for a high share of the overall medical radiation exposure.[1311]

In order to minimize radiation exposure during cardiac radionuclide imaging, it is important to use small doses in pediatric patients, use Tc myocardial perfusion agents, encourage post-test fluid intake and early voiding, and use the minimum dose that provides useful images for diagnostic purposes.[236] In Japan, the relationship between image quality and the appropriate radiopharmaceutical dose is described in the consensus guidelines for nuclear medicine examination in children.[1308] It is also necessary to be aware of the characteristics of nuclear medicine studies. For example, the effective dose per unit dose and radiosensitivity both increase as the patient becomes younger. In addition, the half-life of Tl-201is very long at 73 hours, compared with 6 hours for Tc myocardial perfusion agents.

### 8.4.4 Pharmacological Stress Drugs

Pharmacological stress and resting myocardial perfusion SPECT is an important method for detecting coronary artery stenosis caused by KD.[1312] In Japan, adenosine is approved for nuclear medicine studies and is the main agent used for pharmacological stress. Usefulness of adenosine stress loading for evaluation of coronary stenosis caused by KD has been reported.[1313] Adenosine causes minor adverse reactions, but the incidence is high.[244] However, given its short half-life of less than 10 s, it is useful for infants and young children, who tend to complain of symptoms less often and are therefore more likely to have latent disease.

### 8.4.5 Myocardial Perfusion Imaging With Tc Myocardial Perfusion Agents

An imaging protocol using Tc myocardial perfusion agents (Tc-99 m sestamibi or Tc-99 m tetrofosmin) has been proposed for coronary stenosis due to KD.[1314] The consensus guidelines for nuclear medicine examination in children should be consulted for the recommended dose.[1308] In order to obtain good images, the following points should be taken into consideration: (1) careful attention should be paid to avoiding body movement at the time of imaging, and repeat imaging must be considered if movement artifacts are found after imaging; (2) the maximum stress load should be maintained for ≥1 min following administration of a radiopharmaceutical for stress imaging; (3) excretion from the liver and gallbladder should be promoted by eating and drinking egg products, milk, and cocoa after administration of Tc myocardial perfusion agents; (4) imaging should be performed ≥30 min after administration of the radiopharmaceutical so that liver accumulation has washed out; (5) adopting a backstroke position with the left upper extremity raised (Monzen posture) during imaging minimizes artifacts at sites adjacent to liver accumulation;[1315] and (6) drinking soda immediately before imaging distends the stomach and reduces artifacts at sites adjacent to intestinal accumulation.

### 8.4.6 ECG-Gated Acquisition

ECG-gated acquisition allows simultaneous analysis of myocardial blood flow and cardiac function. Indices that can be analyzed by this method include left ventricular wall motion, the wall thickness change rate, left ventricular volume, LVEF, and left ventricular diastolic function. Postischemic myocardial stunning[1316] can be investigated in patients with severe coronary artery lesions due to KD and the viability of infarcted myocardium can be assessed.[1303,1317] There are limitations on using this method in patients with a small heart (diastolic volume ≤≈50 mL), who are generally aged 6 years or younger.

### 8.4.7 Appropriate Radiopharmaceutical Dosages

According to the Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases by the Japanese Circulation Society,[1318] the general formula for determining

the pediatric dosage of a radiopharmaceutical is as follows: pediatric dosage = adult dosage × (age + 1)/(age + 7). In 2013, the Japanese Society of Nuclear Medicine issued consensus guidelines for nuclear medicine examination in children,[1308] making it possible to calculate recommended doses for each radiopharmaceutical. As shown in **Table 60**,[1308] the appropriate dose of a radiopharmaceutical can be calculated as the product of the "Basic dose established for each radiopharmaceutical" and the "Coefficients set by weight for each class".

**Table 60. Calculation of Appropriate Pediatric Doses of Radiopharmaceuticals**

| |
|---|
| **Example 1: Dose of Tc-99m tetrofosmin for 20 kg body weight (2-day myocardial protocol)** |
| 63.0 (basic dose) × 4.86 (coefficient) = 306, which is <592 (maximum dose) |
| Thus, 306 MBq is administered (based on the assumption that the adult dose is 592 MBq) |
| **Example 2: Initial dose of Tc-99m MIBI for 10 kg body weight (1-day myocardial protocol)** |
| 28.0 (basic dose) × 2.71 (coefficient) = 76, which is <80 (minimum dose) |
| Thus, 80 MBq is administered |
| **Example 3: Second dose of Tc-99m MIBI for 10 kg body weight (2-day myocardial protocol)** |
| 84.0 (basic dose) × 2.71 (coefficient) = 228, which is >160 (minimum dose) |
| Thus, 228 MBq is administered |

(Reproduced from Koizumi et al 2014,[1308] with permission.)

## 8.5 CCTA

### 8.5.1 Target Diseases

#### a. Kawasaki Disease

With regard to diagnostic imaging for follow-up of coronary artery lesions due to KD, the AHA recommended in 2017 that the testing methods and intervals should be determined on the basis of the internal diameter of the coronary artery aneurysm.[1280,1295] For patients with small or larger coronary artery aneurysms (z score ≥2.5), including medium and giant aneurysms, CCTA, coronary MRA, and selective coronary angiography receive a Class IIb recommendation with evidence level C, and are described as "further imaging" methods that "may be considered". It is reasonable to perform CCTA and other morphological evaluations less frequently than stress testing for ischemia. It is recommended to consider CCTA every 3–5 years in patients with small coronary artery aneurysms, every 2–5 years in patients with medium coronary artery aneurysms, and once within 6 months of onset and every 1–5 months thereafter in patients with giant coronary artery aneurysms.

CCTA has the advantage over coronary MRA of allowing observation of the entire coronary artery, including peripheral lesions. Although the disadvantages are radiation exposure and the need to use $\beta$-blockers as premedication for heart rate control, the latter has a short half-life intravenous $\beta$-blocker can be safely used in children with a high heart rate.[1319] In younger children, CCTA is easier to perform from the viewpoint of sedation.[1320] Other advantages of CCTA over coronary MRA are the shorter acquisition time and no requirement for special techniques to perform imaging and image reconstruction. The short imaging time and the fact that sedation is not needed are highly significant for children.

Severe calcification is a characteristic of coronary artery lesions caused by KD, and it is one of the main reasons for false-positive findings on CCTA.[1321] Thanks to improvements in CT equipment, however, diagnostic performance has become much better. CCTA is important for detection of ischemic lesions associated with coronary artery aneurysms and severe coronary artery stenosis.[1322] CCTA uses contrast medium to depict blood flow, and is useful for evaluating the collateral circulation that characteristically develops after the onset of KD. It was reported that CCTA might be more useful than selective coronary angiography for evaluating collateral circulation associated with total occlusion, although the study was not specifically about KD.[1323]

#### b. Coronary Artery Anomalies

The guidelines for appropriate use of cardiac CT from the 8 major American societies state that CT is the most appropriate test, on a 9-point scale, for assessing coronary artery anomalies in adults.[1324] Coronary artery anomalies show wide variation (**Table 59**),[1287] and interpretation of these anomalies in children requires knowledge of the normal variants of coronary artery anatomy. A study of coronary artery anatomy in 543 patients undergoing CCTA showed that variations in the number of diagonal and obtuse marginal arteries were common, with 10.9% and 3.3% of patients having a myocardial bridge and absent left main trunk (i.e., the left anterior descending artery and left circumflex artery originated directly from the aorta), respectively.[1325] Regarding anomalies of coronary artery size, right coronary artery dominance accounts for 89%.[1326]

#### c. Congenital Heart Disease

CCTA can be used for preoperative assessment of the coronary arteries in patients with congenital heart disease, as described above, and can also be used after a patient has undergone coronary artery transplantation by the Ross or Jatene procedure.

#### d. Chronic Coronary Heart Disease Associated With Diseases Other Than KD

Takayasu's arteritis is a systemic vasculitis that is commonly known as macroangiitis.[1327] According to a case report, an adult patient, not a child, with Takayasu's arteritis had coronary lesions.[1328]

### 8.5.2 Radiation Exposure

As dual-source CT and area-detector CT have become widely available, the radiation exposure from CCTA has declined rapidly, making it suitable for follow-up examination even in infants and young children. The effective doses delivered by 3 types of CT scanners were studied in persons aged ≤18 years, revealing that it was 6.8 mSv for 64-row MDCT, 2.9 mSv for 64-row dual-source CT, and 1.0 mSv for 128-row dual-source CT. One of the reasons for the reduction in the exposure dose is use of high-pitch prospective ECG gating.[1329] For infants and young children, it is also important to reduce radiation exposure by using low tube voltage imaging at 80 kV.[1330]

When calculating the effective dose (mSv) for children, conversion factors for the effective dose cannot be used with the same dose–length product as for adults. Conversion

**Table 61. Coronary Artery Visibility and Data Collection by MRA in Children**

| Author | No. of patients | Age (mean) | Magnetic field strength | No. of sequenced coil channels | Method/ imaging area | Contrast medium | Sedation | Coronary artery visualization (coronary artery - reference) |
|---|---|---|---|---|---|---|---|---|
| Taylor et al[1337] | CHD (TGA), 16 | 8.7–14.1 (10.8) | 1.5 | SSFP 5 | FB/target | Gd-DTPA 0.2 mmol/kg | General anesthesia (1/16) | Proximal site, 72% (surgical findings) |
| Mavrogeni et al[1338] | KD, 20 | 7–12 (NR) | 1.5 | GRE 5 | FB/target | None | None | Overall, 100% (CAG) |
| Greil et al[1339] | KD, 6 | 2.5–7.8 (4.6) | 1.5 | SSFP 5 | FB/whole heart | None | Propofol, midazolam | Overall, 100% (CAG) |
| Takemura et al[1336] | KD, 35 | 0.6–6.6 (3.6) | 1.5 | SSFP (NR) | FB/target and whole heart | None | Triclofos sodium syrup + thiopental sodium | Proximal site, 86–97%; Overall, 60% (none) |
| Beerbaum et al[1335] | CHD, 40 | 2.6–25.8 (14.1) | 1.5 | SSFP 5 | FB/whole heart | None | General anesthesia (10/40) | Proximal site, 90% (CAG, 12) |
| Tangcharoen et al[1334] | CHD, 100 | 0.2–11 (3.9) | 1.5 | SSFP 2–5 | FB/whole heart | Gd-DTPA 0.2 mmol/kg | General anesthesia | Overall, 79% (surgical findings, 58) |
| Rajiah et al[1333] | CHD, 112 | 0.03–68 (17) | 1.5 | SSFP (NR) | FB/whole heart | None | Yes (<7 years) | Proximal site, 99% (CAG, 13%; CCTA, 2%) |
| Tacke et al[1340] | KD, 63 | 12.5–18.6 (14.6) | 1.5 | SSFP (NR) | FB/whole heart | None | None | Proximal site, 100% (None) |
| Kim et al[1341] | KD, 17 | 0.2–24 (14) | 1.5 | SSFP 5/32 | FB/target and whole heart | None | NR | Overall, 74% (CCTA) |
| Hussain et al[1342] | CHD, 48; KD, 1; CM, 1 | 0.05–18 (4) | 1.5 | SSFP 2–5 | FB/target and whole heart | None | General anesthesia | Superior to echocardiography (angiogram or surgical record) |
| Silva Vieira et al[1343] | CHD, 40 | 2–12 (6) | 1.5 | SSFP 5 | FB/whole heart | None/ Gd-BOPTA | General anesthesia | Without contrast medium, 87%, With contrast medium, 90% (none) |

CAG, coronary angiography; CCTA, coronary CT angiography; CHD, congenital heart disease; CM, cardiomyopathy; FB, free-breathing; Gd-BOPTA, meglumine gadopenate; Gd-DTPA, gadoxetate disodium; GRE, gradient echo; KD, Kawasaki disease; NR, not reported; SSFP, steady-state free precession; TGA, transposition of the great arteries.

factors are set for each body site, age (neonates, 1, 5, 10 years, and adults), and tube voltage (80, 100, 120, and 140 kV). A younger age and lower tube voltage both lead to a larger conversion factor.[1331]

### 8.5.3 FFR-CT

In KD, calcification and stenosis are often noted at the sites of coronary artery aneurysms, and PCI is sometimes performed at a later stage. CCTA has come to play a role as a substitute for invasive, selective coronary angiography when assessing the cardiovascular prognosis,[1332] but the FFR-CT cutoff value for functional ischemia does not precisely correspond to the FFR value.[579] The Japanese Circulation Society has issued guidelines for the appropriate use of HeartFlow FFR-CT, stating that it should not be used for screening, if the patient is not a candidate for revascularization, and if the diameter of the target coronary artery is ≤2 mm.[591] FFR-CT cannot be calculated for small coronary arteries with a diameter ≤2 mm, which limits its application in children.

## 8.6 MRI and MRA

The role of cardiac MRI in the diagnosis of chronic coronary heart disease can be summarized by the following 3 items: evaluation of coronary artery morphology, myocardial tissue characterization, and evaluation of cardiac function and wall motion. Cardiac MRI was initially established in adults, but the objectives of examination and imaging techniques are different for children. This section describes the application of cardiac MRI in children.

### 8.6.1 Evaluation of Coronary Artery Morphology

In adults, the primary objective of evaluating coronary artery morphology is to detect significant stenosis associated with arteriosclerosis. Currently, whole-heart coronary MRA using the steady-state free precession (SSFP) sequence without breath-holding is the mainstream imaging method. According to the latest systematic review and meta-analysis, coronary MRA has a sensitivity of 89% and specificity of 72% for detection of significant stenosis, and the sensitivity is even higher with contrast enhancement (95% vs. 87% without contrast).[634] On the other hand, the primary purpose of coronary artery imaging in children is to identify the origin and course of the arteries in patients with congenital heart disease, and to assess aneurysms and stenosis in patients with KD. In children, image quality is highly dependent on body size and heart rate.[1333,1334]

**Table 61** lists the recent literature on the visibility of coronary MRA in children. According to an in-depth analysis of 100 neonates and children with congenital heart disease,[1335] the time available for coronary MRA data collecting was not influenced by age or heart rate at end-systole, but was shorter at mid-diastole in the younger

group, and it was recommended that mid-systole be set for collection of data in children aged ≤2 years. Delineation of the coronary arteries was possible in 84 children, including 1 of 6 (17%) among those aged <4 months vs. 83 of 94 (88%) among those aged > 4 months. Another study of coronary MRA in 112 patients with congenital heart disease reported that the coronary artery origins were identified in 99%, although image quality was inferior in younger patients.[1333] Among 40 patients with congenital heart disease undergoing coronary MRA, the origin and proximal course of the right coronary artery were identified in all 40 patients, while this was achieved for the left main trunk and left anterior descending artery in 38 patients, and for the left circumflex artery in 36 patients.[1335] Segmental visualization was investigated in 35 patients with KD undergoing coronary MRA, showing that evaluation of the right coronary artery and the left main trunk and proximal left anterior descending artery was possible in 97%, while the proximal left circumflex artery was assessable in 91%.[1336] In 16 patients with complete transposition of the great arteries who had undergone the Jatene procedure, coronary MRA obtained useful images of 23 of 32 coronary arteries (72%).[1337]

As conditions such as the use of contrast medium, sedation, and controlled respiration vary from case to case, a simple judgment cannot be made. However, if scanning is performed under certain conditions in children aged ≥4 months, evaluation of the origin and proximal course of the coronary arteries is possible. There is consensus that the same imaging protocols used for adults are sufficient for patients aged ≥8 years who do not require sedation.[1333–1343]

### 8.6.2 Evaluation of the Myocardium

Investigation of myocardial characteristics by cardiac MRI mainly involves pharmacological stress perfusion studies for evaluation of ischemia and late gadolinium enhancement (LGE) to assess myocardial viability and inflammation. Adenosine is commonly used for stress perfusion studies, with dipyridamole as an alternative. In adults, a meta-analysis demonstrated diagnostic accuracy of cardiac MRI for ischemia, with a sensitivity of 90% and specificity of 85% compared with FFR.[1344]

Cardiac MRI has also been reported as useful for detecting ischemia in children, with a positive predictive value of 80% and negative predictive value of 88% compared with coronary angiography, as well as a positive predictive value of 78% and negative predictive value of 98% for MACE during 1-year follow-up.[1345] Another study showed that 4 of 15 children with KD and coronary artery aneurysms developed stress perfusion defects (5 had LGE), suggesting the usefulness of comprehensive evaluation by cardiac MRI, including coronary MRA/myocardial properties/wall motion.[1340]

Investigation of LGE is used for delineation of infarcts and assessment of myocardial viability in patients with KD,[1338,1340] and in patients who have undergone the Jatene procedure for complete transposition of the great arteries.[1340] Assessment of LGE is useful for differentiation of ischemic and nonischemic cardiomyopathy based on its distribution and extent,[1346] and this imaging method is fundamentally handled the same way as in adults.

### 8.6.3 Evaluation of Ventricular Function and Wall Motion

Imaging is performed the same way as in adults to quantify wall motion, volumes, and cardiac mass.[1347] Usually, images are obtained with breath-holding, but when sedation is required in a child who cannot cooperate, motion artifacts should be reduced by partly fixing the abdomen to minimize chest movement during respiration and by summation of ≥2 images.

### 8.6.4 Sedation

In infants under 6 months old, scanning is possible during sleep after breast feeding,[1348] but the scanning protocol should be compatible with shallow sleep and a short imaging time. As shown in **Table 61**, deep sedation is also useful,[1349] but adequate monitoring is required to avoid the risk of hypoventilation or aspiration. The Joint Declaration of the Japan Pediatric Society, Japanese Society of Pediatric Anesthesiology, and Japanese Society of Pediatric Radiology on sedation for MRI provides further details.[1350] Imaging under general anesthesia allows breath-holding and is very safe if performed by a trained team.[1351–1353] However, it requires the services of an anesthesiologist and special medical devices that can be used in a magnetic field, and is accordingly quite expensive.

### 8.6.5 No Radiation Exposure

The disadvantages of cardiac MRI are its high cost and long imaging time, while its advantages are no radiation exposure and contrast medium is not always required. Recent large-scale studies have shown that exposure to even low doses of radiation at a young age is associated with an increased risk of cancer. For example, the risk of leukemia was increased by a dose of 0.036/mGy,[1354] and there was a 24% increase in the risk of cancer per CT scan during a 9.5-year follow-up period.[1355] Hence, there is a significant benefit in using cardiac MRI for children who require follow-up with repeat imaging.

### 8.6.6 Other Considerations

The presence of implanted medical devices should be determined before MRI, whether cardiac or not.[1356] When the history is unclear and an implanted device may potentially be present, simple X-ray examination of the whole body is useful. Gadolinium contrast media may also cause problems. Although the risk is generally lower than with iodinated contrast media, attention should be paid to allergic reactions that can range from extravasation to wheals and even anaphylaxis.[1357–1359] Therefore, written consent to use contrast medium should be obtained before testing. NSF has also been reported as a serious complication. It is characterized by progressive, untreatable, and life-threatening widespread fibrosis affecting the skin, subcutaneous tissues, joints, skeletal muscles, and internal organs. NSF usually occurs in patients with renal impairment and an eGFR <30 mL/min/1.73 m$^2$. Other risk factors for NSF include renal transplantation, concurrent hepatic disease, and pre-inflammatory conditions.[1360,1361] However, NSF is extremely rare, and is even less frequent in children than adults.[1362] Because of the low incidence of NSF among neonates and infants, despite their immature renal function, some centers use high doses of gadolinium contrast media, but it is preferable to use the lowest possible dose.

Moreover, it was recently reported that gadolinium contrast media can accumulate in the brain.[1363–1365] Metallic gadolinium is toxic, but there have been no reports about toxicity when it is administered as a contrast agent, except for NSF. There was no increase in the incidence of treatment-related Parkinson's disease among 99,000 patients

who received gadolinium contrast agents compared with 146,000 patients who did not.[1366] Also, pathological examination of the brain at autopsy showed no degeneration after administration of gadolinium contrast medium.[1364] The European Medicines Agency suggested discontinuation of the marketing of linear gadolinium contrast media in March 2017.[1367] On the other hand, the US FDA issued a safety declaration 2 months later stating that gadolinium contrast media are not harmful to health,[1368] but then issued a new warning in December 2017.[1369] Thus, no consensus has been reached, even among experts, so it is necessary to carefully assess future developments.

Another safety consideration is protection of the ears, especially in neonates and infants, to avoid auditory damage from the loud noise associated with MRI.[1370] Some centers ensure that infants wear headphones as well as earplugs. Infants and young children are predisposed to develop hypothermia or hyperthermia during examination,[1371] and therefore monitoring of body temperature is important.

#### 8.6.7 Clinical Application

The AHA Guideline for KD[1295] mentions the role of cardiac MRI in evaluation of the cardiovascular system. Because this disease generally affects infants, echocardiography under sedation is the standard method for assessment of coronary artery diameter and ventricular and valvular function in the acute phase. However, cardiac MRI is also indicated in later childhood, when visualization may be decreased if coronary abnormalities such as aneurysm formation are present. Evaluation of coronary artery morphology by coronary MRA is positioned as follows: "should be considered when symptomatic in patients whose coronary artery diameter has returned to normal, and should be considered periodically in patients with aneurysms or residual enlargement (Recommendation Class IIb)." On the other hand, evaluation of the myocardium (mainly assessment of ischemia by perfusion studies) is described as "should be considered when symptomatic regardless of coronary artery diameter (Recommendation Class IIa)."

The background to such guidance is that cardiac MRI is expensive and technically complex with limited evidence. Nevertheless, it may be useful for routine follow-up from later childhood onwards, because of its major advantage of no radiation exposure. As the anomalous origin of a coronary artery is an important cause of sudden death among juveniles, it is expected that the indications for cardiac MRI may be eventually expanded to screening for school children and athletes.

#### 8.6.8 Future Challenges

When cardiac MRI is used for assessment of chronic coronary heart disease in children, the imaging method and performance vary according to the patient, examiner, and equipment. Therefore, clinicians ordering these tests should be aware of which patients are suitable and to what extent testing is feasible. Cardiac MRI is especially challenging in the neonatal period and early infancy, when the patient is very small and the heart rate is high. However, no use of contrast agents, no radiation exposure, and noninvasiveness are significant advantages, especially in children, who have a high sensitivity to radiation and a long life expectancy. It is necessary for workers involved in the pediatric cardiovascular field to make efforts to establish more appropriate testing methods based on thorough understanding of these points.

### 8.7 Cardiac Catheterization

#### 8.7.1 Coronary Angiography

Coronary angiography via cardiac catheterization is the gold standard for accurate diagnosis of chronic coronary heart disease in children. It is indicated for patients with moderate or severe coronary artery aneurysms, coronary stenosis or occlusion, and coronary artery anomalies (origin and course), etc., and it is particularly indicated in the case of catheter treatment or surgery being considered. Additional tests may also be performed, such as measurement of the coronary artery pressures or coronary flow velocity and IVUS.

On the other hand, the disadvantages of cardiac catheterization are invasiveness and radiation exposure. There is a risk of thromboembolism, perforation, vascular injury, and arrhythmia during the procedure, as well as postprocedural peripheral circulatory failure at the puncture site and pseudoaneurysm. General anesthesia may also pose a risk in young children. Use of cardiac catheterization is only recommended if less invasive assessment using CCTA or MRA is impossible.

#### 8.7.2 Measurement of Intracoronary Pressure, FFR, and Coronary Flow Velocity

Measurement of pressure and blood flow velocity is mainly performed for coronary artery lesions in patients with KD. Small aneurysms show normal time-averaged blood flow velocity, CFR, and shear strength, whereas giant aneurysms generate turbulent flow with a decrease in the time-averaged blood flow velocity, CFR, and shear strength.[1372] FFR and CFR are decreased at sites of significant coronary stenosis and show improvement after PCI or CABG.[1373]

#### 8.7.3 IVUS and OCT

IVUS and OCT delineate the structure of the coronary artery wall by using echo signals and near-infrared light, respectively, and can be used to observe intimal thickening, luminal stenosis, thrombi, and calcification. In a study of coronary artery aneurysms in patients with KD,[1283] intimal thickening was frequently observed in vessels with an internal diameter ≥4 mm. Virtual histology IVUS allows tissue characterization at sites of intimal thickening, including fibrosis, calcification, lipid components, and necrosis.[1374] There has been a similar report concerning OCT in children,[1375] so further studies are warranted to investigate the relationship of these findings with long-term arteriosclerotic lesions and cardiovascular events. Recommendations and levels of evidence for diagnosis of children at risk for coronary heart disease are shown in **Table 62**.

## 9. Diagnosis of Polyvascular Disease

### 9.1 Polyvascular Disease

It has recently attracted attention that coronary heart disease can be associated with cerebrovascular disease and/or PAD of the lower extremities. These conditions all originate from systemic arteriosclerosis (atherothrombosis), and it has been advocated that patients with involvement of multiple vascular beds should be comprehensively managed under the designation of polyvascular disease (multivascular disease and systemic arteriosclerosis).[1376] A

**Table 62. Recommendations and Levels of Evidence for Testing Methods to Diagnose and Assess Children at High Risk for Coronary Heart Disease (Kawasaki Disease, etc.)**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **Exercise ECG** | | | | |
| Asymptomatic Kawasaki disease without coronary lesions | IIb | C | C1 | V |
| Asymptomatic Kawasaki disease with coronary lesions | IIa | C | B | V |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) | I | C | B | V |
| All patients with a suspected ischemic event | I | C | B | IVb |
| **Resting echocardiography** | | | | |
| Asymptomatic Kawasaki disease without coronary lesions | I | C | A | IVa |
| Asymptomatic Kawasaki disease with coronary lesions | I | C | A | IVa |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) | I | C | A | V |
| All patients with a suspected ischemic event | I | C | A | IVa |
| **Stress echocardiography** | | | | |
| Asymptomatic Kawasaki disease without coronary lesions | IIb | C | C2 | V |
| Asymptomatic Kawasaki disease with coronary lesions | I | C | B | IVa |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) | I | C | B | V |
| All patients with a suspected ischemic event | I | C | B | IVa |
| **Myocardial perfusion imaging** | | | | |
| Asymptomatic Kawasaki disease without coronary lesions | IIb | C | C2 | V |
| Asymptomatic Kawasaki disease with regression of coronary lesions | IIa | C | C1 | V |
| Asymptomatic Kawasaki disease with coronary lesions | I | B | A | IVb |
| (Imaging at rest only): detection of anomalies of coronary artery origin and course (especially preoperative assessment) | IIa | C | C1 | V |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) | I | C | B | V |
| All patients with a suspected ischemic event | I | B | A | IVb |
| **CCTA** | | | | |
| Asymptomatic Kawasaki disease without coronary lesions | IIb | C | C2 | V |
| Asymptomatic Kawasaki disease with regression of coronary lesions | IIa | C | C1 | V |
| Asymptomatic Kawasaki disease with coronary lesions | IIa | C | B | IVb |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) in younger children (approximately <5 years old) requiring sedation | IIb | C | C1 | V |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) in older children (approximately ≥5 years old) requiring sedation | IIa | C | B | V |
| All patients with a suspected ischemic event | IIa | C | B | IVb |

(**Table 62** continued the next page.)

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **Coronary MRA** | | | | |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) in younger children (approximately <7 years old) requiring sedation | IIb | C | C1 | V |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) in older children (approximately ≥7 years old) not requiring sedation | I | C | B | V |
| Asymptomatic Kawasaki disease without coronary lesions | IIb | C | C1 | V |
| Asymptomatic Kawasaki disease with coronary lesions | IIa | C | B | V |
| Kawasaki disease with symptoms suggestive of ischemic events | I | C | A | V |
| Stress myocardial perfusion SPECT: Patients with symptoms suggestive of ischemic events, Kawasaki disease with coronary lesions, and after coronary artery surgery | I | B | A | IVb |
| **LGE** | | | | |
| All patients with a suspected ischemic event | I | C | B | V |
| After the Jatene or Ross procedure, coronary artery anomalies, and after surgery for coronary artery anomalies | I | C | B | V |
| Asymptomatic Kawasaki disease with coronary lesions | IIb | C | C1 | V |
| Asymptomatic Kawasaki disease without coronary lesions | IIb | C | C1 | V |
| Cine MR: All patients with suspected heart disease, including Kawasaki disease | I | C | A | IVb |
| **Cardiac catheterization** | | | | |
| Asymptomatic Kawasaki disease without coronary lesions | IIb | C | C2 | V |
| Asymptomatic Kawasaki disease with coronary lesions | IIa | C | B | IVa |
| Detection of anomalies of coronary artery origin and course (including assessment after the Jatene or Ross procedure) | IIa | C | B | V |
| All patients with a suspected ischemic event | I | C | B | IVa |

CCTA, coronary computed tomography angiography; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

prospective multicenter observational study of atherothrombosis (REACH Registry), showed that patients with atherothrombosis in the coronary, cerebral, or peripheral arteries often also have lesions in other vascular beds.[1377–1379]

It is important to note that the prognosis of patients with polyvascular disease is poor. A follow-up investigation of the REACH Registry study showed that the 1-year incidence of cardiovascular events increased with the number of affected vascular beds in patients with polyvascular disease.[1167] Specifically, the incidence of cardiovascular events was 12.58% in the case of 1 vascular bed being involved, but increased to 21.14% when 2 beds were involved and to 26.27% when 3 beds were involved. Thus, the incidence of events increased significantly along with the number of vascular beds involved ($P<0.001$). Furthermore, multivariate analysis of 4-year follow-up data from the REACH Registry showed that polyvascular disease was the most important risk factor for development of cardiovascular events (hazard ratio: 1.99; 95% CI: 1.78–2.24).[1380] Therefore, it is important to always be aware of the possibility of polyvascular disease when managing patients with coronary artery disease. It is also important to explore the possibility of polyvascular disease, including coronary artery disease, in patients who have cerebrovascular disease or PAD.

## 9.2 Cerebrovascular Disease (Table 63)

### 9.2.1 Significance as a Component of Polyvascular Disease

Cerebrovascular disease can be divided into ischemic cerebrovascular disorders (cerebral infarction and transient ischemic attack) and hemorrhagic cerebrovascular disorders (cerebral hemorrhage and subarachnoid hemorrhage). In Japan, the annual number of deaths from cerebrovascular disorders is ≈110,000, and it is the fourth highest cause of death.[1381] It is also the second most important reason for patients to require nursing care (18.4%).[1382] Prevention and appropriate treatment of the onset and recurrence of cerebrovascular disease are important.

In the REACH Registry study described above, cerebrovascular disease was identified in 16.9% of patients with coronary heart disease.[1378] It was reported that patients with a history of ischemic cerebrovascular disease have a higher incidence of recurrent cardiovascular events (adjusted hazard ratio: 1.52; 95% CI: 1.40–1.65) than those without

**Table 63. Recommendations and Levels of Evidence for Testing Methods to Diagnose Cerebrovascular (Carotid Artery) Disease**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| **Asymptomatic screening** | | | | |
| Ultrasonography | I | A | A | I |
| CTA | IIb | C | C2 | VI |
| MRA | IIa | A | B | I |
| Angiography | III | C | C2 | VI |
| **Symptomatic detailed examination** | | | | |
| Ultrasonography | I | A | A | I |
| CTA | I | A | B | I |
| MRA | I | A | B | I |
| Angiography | I | A | A* | II |

*Recommended on a case-by-case basis. COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

such a history. Interestingly, patients with a history of ischemic cerebrovascular disease have a higher incidence of nonfatal cerebral infarction (adjusted hazard ratio: 3.06; 95% CI: 2.62–3.57).[1383] Hence, it is important to prevent the recurrence of cerebrovascular disease as well as coronary heart disease.

### 9.2.2 Symptoms and Physical Findings

The sudden onset of hemiplegia is the most typical symptom. However, various symptoms can occur, such as dysarthria, visual disorders, headache, nausea and vomiting, vertigo, and disturbance of consciousness. Accordingly, the potential development of cerebrovascular disorders should be considered in various situations. Patients with early cerebral infarction should receive prompt attention because they can be treated with intravenous recombinant tissue plasminogen activator (rt-PA) or intravascular therapy using a stent retriever.

### 9.2.3 Imaging Studies

Screening for cerebrovascular disease is performed by a combination of carotid ultrasound, head CT, head MRI, head and neck MRA, and/or CTA. Depending on the patient's condition, cerebral perfusion scintigraphy or cerebral angiography may be added.

#### a. Carotid Ultrasound

Carotid ultrasonography is indicated under the following circumstances: (1) for diseases frequently associated with carotid stenosis and obstructive lesions or clinical findings suggestive of such diseases (hemiparesis, arterial bruit, diminished pulse, etc.); (2) when risk assessment is needed before invasive treatment of arteriosclerotic disease in other regions; and (3) in the presence of risk factors for arteriosclerosis and the potential for progression of arteriosclerosis.[1384]

For evaluation of arteriosclerotic lesions, the maximum IMT of the right and left common carotid arteries, carotid bulb, and internal carotid arteries is measured. Assessment of stenosis in the common carotid artery is based on the severity of area stenosis, with diameter stenosis also being determined if necessary. For the internal carotid artery, the severity of stenosis is determined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. Measurement of blood flow (maximum blood flow rate, etc.) at the site of stenosis is also performed.[1384]

#### b. CT

CT can be performed quickly. By using a contrast agent, it is possible to assess the presence and severity of stenosis, as well as the luminal morphology. Although calcification can be detected sensitively, observation of the lumen is difficult at sites of severe calcification. Disadvantages of CT include the risks associated with use of iodinated contrast medium and exposure to radiation. Indications for performing CTA in patients with cerebrovascular disease include arterial stenosis, aneurysms, arteriovenous malformations, sinus thrombosis, and dissection. Regarding the diagnostic accuracy for 70–99% stenosis at the carotid bifurcation, the sensitivity and specificity of CTA were reported to be 68% and 77%, respectively.[1385]

#### c. MRI

MRI is used to evaluate the vessel lumen and wall. It allows visualization of the lumen without contrast agents by the TOF technique. Disadvantages of MRA include the long scan time, restrictions on use of equipment in the examination room/laboratory, and difficulty with interpretation of images due to artifacts. Although contrast medium may be used (contrast-enhanced MRA), the risks associated with gadolinium contrast media should be considered. In addition to the abovementioned indications for CTA in cerebrovascular disease, MRA can be used to screen for cerebral aneurysms and stenotic lesions.

Regarding the diagnostic accuracy for 70–99% stenosis at the carotid bifurcation, the sensitivity and specificity of MRA using the TOF technique without contrast medium were reported to be 76% and 86%, respectively, and contrast-enhanced MRA had a sensitivity and specificity of 86% and 91%, respectively.[1385] The sequences for detecting vulnerable plaques in the carotid artery include T1-weighted, T2-weighted, and proton-density-weighted images, and these are often evaluated in combination. Magnetization prepared rapid acquisition with gradient echo (MPRAGE) is a T1-weighted imaging method that suppresses fat and blood flow signals, and it depicts plaque complicated by hemorrhage as a high signal area.[1386]

#### d. Cerebral Angiography

Angiography involves advancing the catheter to the desired vessel for selective imaging. It provides images with excellent spatial and temporal resolution, but is an invasive test. Although it was reported that the risk of complications from cerebral angiography in patients with ischemic cerebrovascular disease is only in the order of a few percent,[1387] this rate may be higher if asymptomatic cases are included.[1388] Thus, the indications for angiography should be rigorously determined, and it is primarily limited to patients who require intravascular treatment and detailed perioperative assessment.

**Table 64. Recommendations and Levels of Evidence for Testing Methods to Diagnose PAD**

| | COR | LOE | GOR (MINDS) | LOE (MINDS) |
|---|---|---|---|---|
| ABI | I | B | B | IVa |
| TBI | IIa | C | C1 | IVb |
| Ultrasonography | I | C | B | IVb |
| CTA | I | C | B | IVb |
| MRA | I | C | B | IVb |
| Angiography | I | C | C1 | VI |

COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

## 9.3 Peripheral Arterial Disease (Table 64)

### 9.3.1 Significance as a Component of Polyvascular Disease

The representative type of chronic peripheral obstructive arterial disease is ASO, which is caused by arteriosclerosis. The incidence of ASO has been increasing since the mid-1970s, overtaking thromboangiitis obliterans (so-called Buerger's disease),[1389] and it now accounts for a large part of PAD. In fact, the terms PAD and ASO are currently used almost synonymously. Among patients who have polyvascular disease associated with atherothrombosis, PAD is found in approximately half (55.3% in the REACH Registry;[1378] 49.5% in Japan[1379]).

Conversely, approximately half of PAD patients have polyvascular disease (61.5% in the REACH Registry;[1378] 43.8% in Japan[1379]). This is higher than the prevalence of polyvascular disease in patients with coronary heart disease or cerebrovascular disease. Accordingly, the possibility of polyvascular disease should always be considered in PAD patients when plans for investigation are formulated. It should also be kept in mind that the all-cause mortality rate of patients with critical limb ischemia is as high as 80% at 5 years after an initial diagnosis.[1389]

### 9.3.2 Symptoms and Physical Findings

The diagnosis of PAD can often be made by taking a history, physical examination (inspection and palpation), or simple tests. It occurs most frequently in men aged ≥50 years. The characteristic symptom is intermittent claudication, and skin ulcers and necrosis can develop in severe cases. Symptoms include thinning of the affected extremity, decreased skin temperature and a difference from the other leg, skin pallor and cyanosis, nail deformity, hair loss, weak/absent pulses of the common femoral artery, popliteal artery, posterior tibial artery, and dorsalis pedis artery, a palpable thrill, and a vascular murmur. Control of risk factors is essential, and the presence/absence of smoking, diabetes mellitus, hyperlipidemia, or hypertension should be investigated accordingly.[1389]

### 9.3.3 Investigations

Among the following investigations, limb blood pressure measurement and imaging are usually combined. In addition to determining the ABI, an imaging test is essential. The appropriate test should be chosen according to the disease condition, with priority being given to minimally invasive methods.

#### a. Limb Blood Pressure Measurement

##### i) ABI

The ABI is used as an essential diagnosis of PAD, which is calculated as the systolic blood pressure at the ankle (posterior tibial artery and dorsalis pedis artery) divided by the higher of the right or left brachial systolic blood pressures. If the ABI is ≤0.90, significant stenosis of the main limb artery is suspected. If the ABI is >1.40, it indicates that the compression by a tourniquet is insufficient and the existence of severe arterial calcification is suspected.[1389] The ACC/AHA guidelines define an ABI of 0.91–0.99 as the threshold value.[1390] The ABI under exercise testing is used to assess the severity of intermittent claudication and to exclude neurogenic claudication.

##### ii) Toe Blood Pressure and TBI

Because calcification of the toe arteries is less severe than at the ankle, the TBI is more likely to provide accurate data than the ABI in patients who have severe arterial calcification, such as those with renal failure or diabetes mellitus. The cutoff value of the TBI is 0.6–0.7.[1391]

#### b. Imaging Studies

Conventionally, invasive angiography was the main modality of screening and preoperative assessment for PAD, but ultrasound, CT, and MRI have come to play a central role in recent years.

##### i) Ultrasound

Ultrasound is a noninvasive examination that can be performed at the bedside without exposure to radiation or use of contrast medium. In addition to evaluating the vessel wall and lumen, assessment of hemodynamics is available by the color Doppler or pulse Doppler method utilizing the high temporal resolution of ultrasound. Especially in patients with a morphologically borderline lesion, ultrasound is crucial for assessing whether stenosis is hemodynamically significant or not. However, ultrasound has some disadvantages: imaging quality depends on the skill of the technician, there can be difficulty in observing the iliac artery if there is massive bowel gas, and difficulty in overall and definitive assessment of the femoral artery due to the length of the observation area.[1391]

##### ii) CT

CT is a minimally invasive imaging modality, but it involves exposure to radiation and there is a risk of complications associated with use of iodinated contrast medium. CT is recommended in assessing vascular disease because of simultaneous assessment of the great vessels and parenchymal organs in addition to evaluation of the peripheral vasculature.[1392] Both noncontrast CT scans and scans performed in the early contrast phase are required, because noncontrast scanning is crucial for assessing calcification of the arterial wall, whereas the vessel lumen is assessed on early contrast phase scans. In relation to the diagnostic performance of CTA using an MDCT scanner with 16 rows or more, the sensitivity and specificity were reported to be 95–99% and 94–98%, respectively.[1393,1394] Although CT is useful for evaluating vessel wall properties, including

calcification, accurate assessment of the lumen may be difficult in patients with heavily calcified lesions or with stents. To overcome this weakness, new imaging methods such as subtraction techniques have been developed.[1395–1397]

### iii) MRI

MRI has the advantage of being able to evaluate the vessel lumen without using radiation and is not influenced by calcification; however, its spatial resolution is inferior to CT. Moreover, MRI may be contraindicated in patients with a medical device or implant, so confirmation of safety is crucial.[1391]

Imaging sequences for the diagnosis of PAD can be divided into contrast-enhanced MRA and noncontrast-enhanced MRA. With a sensitivity of 97% and specificity of 96%, the diagnostic accuracy of contrast-enhanced MRA is comparable to that of CTA.[1398] Contrast-enhanced MRA is less susceptible than noncontrast-enhanced MRA to the influence of blood flow velocity, direction, and turbulence, and relatively rapid imaging of a wide area is possible.[1391] On the other hand, use of gadolinium contrast media comes with a risk of NSF,[1399] and alternative modalities should be considered in patients with renal dysfunction. Use of contrast-enhanced MRA should be carefully decided because many patients with PAD are elderly and have poor renal function.

Noncontrast-enhanced MRA is an alternative to contrast-enhanced MRA for assessment of lower limb arteries without using contrast medium. In addition to the conventional time-of-flight technique, methods such as fresh blood imaging are applied clinically. Compared with contrast-enhanced MRA, the sensitivity and specificity of noncontrast-enhanced MRA are reported to be 85.4%, and 75.8%, respectively.[1400] However, it has limitations regarding accurate delineation of small arterial lesions and assessment of luminal changes in metallic stents.[1394,1401]

### iv) Angiography

Angiography can selectively evaluate the vessel lumen after inserting a catheter into the target artery and administrating contrast medium directly into the vessel. It is an invasive procedure with a risk of bleeding and embolic complications. Other risks include exposure to radiation and complications associated with the use of iodinated contrast medium. Angiography is excellent for morphological diagnosis of stenosis and occlusion because of its high spatial resolution. It can also be used to evaluate blood flow dynamics. Furthermore, angiography allows assessment of hemodynamics by measuring the pressure gradient between proximal and distal to a lesion, and is used to guide intravascular treatment.[1391]

## Conclusion

As discussed, recent advances in diagnostic imaging for cardiovascular disease have been remarkable. In fact, the number of noninvasive imaging tests performed for chronic coronary heart disease in clinical practice has been steadily increasing over the past few years. Invasive procedures have also been used in many clinical fields, together with advances in technology. Both invasive and noninvasive methods may be required to provide important information that is directly relevant to understanding the patient's pathophysiological situation and to the selection or monitoring of treatment.

It has also been pointed out that a number of revascularization procedures are performed for lesions detected by noninvasive imaging modalities such as CT, regardless of whether the patient has symptoms or ischemia (functional stenosis), raising alarm over increased healthcare expenditure due to advances in medical care. In recent years, confirmation of the existence of ischemia has been required before revascularization is performed in patients with chronic coronary heart disease. Accordingly, more efficient use of diagnostic imaging modalities are expected.

Imaging studies should be focused on assisting decisions about treatment and assessing the prognostic impact. However, more large-scale clinical studies are needed to provide sufficient data before imaging can properly fulfill these functions. Although sufficient evidence was not available in the past, a large body of evidence has recently been accumulated in both Japan and other countries. Taking these points into consideration, we compiled this guideline on the noninvasive diagnosis of chronic coronary heart disease, which is the condition with the highest incidence among all cardiovascular diseases, and efficient utilization of invasive examinations on the basis of the available evidence and the current medical practice in Japan. As a new feature, evidence-based recommendations have been added to each entry to facilitate the use of this guideline in clinical practice. Accordingly, we do hope that this guideline will be used in diverse clinical settings.

## References


1. Tamaki N, Kumita S, Kusakabe K, Matsuzaki M, Nishimura T, Senda S, et al; JCS Joint Working Group. Guidelines for clinical use of cardiac nuclear medicine (JCS 2010): Digest version. *Circ J* 2012; **76:** 761–767. PMID: 22293456
2. Yamashina A, Ueshima K, Kimura K, Kuribayashi S, Sakuma H, Tamaki N, et al. Guidelines for noninvasive diagnosis of coronary artery lesions (JCS 2009). *Circ J* 2009; **73**(Suppl III)**:** 1019–1114 (in Japanese). http://www.j-circ.or.jp/guideline/pdf/JCS2010_yamashina_h.pdf (accessed Dec 25, 2019).
3. Fukui T, Yoshida M, Yamaguchi N. *In*: Minds handbook in practical guideline 2007. Tokyo: Igakushoin, 2007; 8–51 (in Japanese).
4. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. *J Atheroscler Thromb* 2018; **25:** 846–984. PMID: 30135334
5. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991; **325:** 849–853. PMID: 1875969
6. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, et al. ACC/AHA guidelines for exercise testing: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997; **30:** 260–311. PMID: 9207652

7. Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease: A meta-analysis. *Circulation* 1989; **80:** 87–98. PMID: 2661056
8. Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Ann Intern Med* 1999; **130:** 719–728. PMID: 10357690
9. Lee TH, Boucher CA. Clinical practice: Noninvasive tests in patients with stable coronary artery disease. *N Engl J Med* 2001; **344:** 1840–1845. PMID: 11407346
10. Pearson TA. New tools for coronary risk assessment: What are their advantages and limitations? *Circulation* 2002; **105:** 886–892. PMID: 11854132
11. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: A Scientific Statement from the American Heart Association. *Circulation* 2013; **128:** 873–934. PMID: 23877260
12. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002; **106:** 1883–1892. PMID: 12356646
13. Schartl M, Beckmann S, Bocksch W, Fateh-Moghadam S, Fleck E. Stress echocardiography in special groups: In women, in left bundle branch block, in hypertension and after heart transplantation. *Eur Heart J* 1997; **18**(Suppl)**:** D63–D67. PMID: 9183613
14. Murayama M, Ohta T, Ohtsu F, Kawakubo Y, Kishida H, Kubota Y, et al; Japanese Society of Electrocardiology. Survey of exercise stress electrocardiogram in Japan. *Jpn J Electrocardiogr* 1996; **16:** 185–208 (in Japanese).
15. Stuart RJ, Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980; **77:** 94–97. PMID: 7351157
16. Bruse RA, Blackmon Jr, Jones JW, Strait G. Exercising testing in adult normal subjects and cardiac patients. *Pediatrics* 1963; **32**(Suppl)**:** 742–756. PMID: 14070531
17. Saito M. *In*: Cardiac disease and exercise stress testing, 2nd edn. Tokyo: Chugaiigakusha, 1993(in Japanese).
18. American College of Sports Medicine. Guidelines for exercise testing and prescription, 3rd edn. New York: Lea & Feibiger, 1986.
19. Borg G. Perceived exertion as an indicator of somatic stress. *Scand J Rehabil Med* 1970; **2:** 92–98. PMID: 5523831
20. Pruvost P, Lablanche JM, Beuscart R, Fourrier JL, Traisnel G, Lombart F, et al. Enhanced efficacy of computerized exercise test by multivariate analysis for the diagnosis of coronary artery disease: A study of 558 men without previous myocardial infarction. *Eur Heart J* 1987; **8:** 1287–1294. PMID: 3325288
21. Myers J, Froelicher VF. Exercise testing: Procedures and implementation. *Cardiol Clin* 1993; **11:** 199–213. PMID: 8508447
22. Cohn PF, Vokonas PS, Herman MV, Gorlin R. Postexercise electrocardiogram in patients with abnormal resting electrocardiograms. *Circulation* 1971; **43:** 648–654. PMID: 5578841
23. Miranda CP, Lehmann KG, Froelicher VF. Correlation between resting ST segment depression, exercise testing, coronary angiography, and long-term prognosis. *Am Heart J* 1991; **122:** 1617–1628. PMID: 1957757
24. Barlow JB. The "false positive" exercise electrocardiogram: Value of time course patterns in assessment of depressed ST segments and inverted T waves. *Am Heart J* 1985; **110:** 1328–1336. PMID: 4072905
25. Ishimura T, Yamaguchi H. Coronary artery stenosis and stress electrocardiogram: Evaluation of coronary angiography. *Sougorinsho* 1977; **26:** 395–403 (in Japanese).
26. Guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommitte on Exercise Testing). *J Am Coll Cardiol* 1986; **8:** 725–738. PMID: 2943787
27. Krone RJ, Miller JP, Gillespie JA, Weld FM. Usefulness of low-level exercise testing early after acute myocardial infarction in patients taking beta-blocking agents. *Am J Cardiol* 1987; **60:** 23–27. PMID: 2886042
28. Kishida H, Hata N, Kanazawa M. Prognostic value of low-level exercise testing in patients with myocardial infarction. *Jpn Heart J* 1989; **30:** 275–285. PMID: 2795868
29. Nielsen JR, Mickley H, Damsgaard EM, Frøland A. Predischarge maximal exercise test identifies risk for cardiac death in patients with acute myocardial infarction. *Am J Cardiol* 1990; **65:** 149–153. PMID: 2296882
30. Stevenson R, Umachandran V, Ranjadayalan K, Wilkinson P, Marchant B, Timmis AD. Reassessment of treadmill stress testing for risk stratification in patients with acute myocardial infarction treated by thrombolysis. *Br Heart J* 1993; **70:** 415–420. PMID: 8260271
31. Villella A, Maggioni AP, Villella M, Giordano A, Turazza FM, Santoro E, et al. Prognostic significance of maximal exercise testing after myocardial infarction treated with thrombolytic agents: The GISSI-2 data-base. *Lancet* 1995; **346:** 523–529. PMID: 7658777
32. Okin PM, Kligfield P. Computer-based implementation of the ST-segment/heart rate slope. *Am J Cardiol* 1989; **64:** 926–930. PMID: 2801562
33. Maehara K, Kinoshita H, Inoue K, Takahashi T, Itoh N, Shimizu Y, et al. Discrimination of false positive ST depression by HR-ST and anaerobic threshold-ST relationships during the exercise test. *Rinsho Byori* 1986; **34:** 1135–1141. PMID: 3100845 (in Japanese). https://www.ncbi.nlm.nih.gov/pubmed/?term=3100845 (accessed Dec 25, 2019).
34. Haines DE, Beller GA, Watson DD, Kaiser DL, Sayre SL, Gibson RS. Exercise-induced ST segment elevation 2 weeks after uncomplicated myocardial infarction: Contributing factors and prognostic significance. *J Am Coll Cardiol* 1987; **9:** 996–1003. PMID: 3571761
35. Margonato A, Chierchia SL, Xuereb RG, Xuereb M, Fragasso G, Cappelletti A, et al. Specificity and sensitivity of exercise-induced ST segment elevation for detection of residual viability: Comparison with fluorodeoxyglucose and positron emission tomography. *J Am Coll Cardiol* 1995; **25:** 1032–1038. PMID: 7897113
36. Lombardo A, Loperfido F, Pennestri F, Rossi E, Patrizi R, Cristinziani G, et al. Significance of transient ST-T segment changes during dobutamine testing in Q wave myocardial infarction. *J Am Coll Cardiol* 1996; **27:** 599–605. PMID: 8606270
37. Correale E, Battista R, Ricciardiello V, Martone A. The negative U wave: A pathogenetic enigma but a useful, often overlooked bedside diagnostic and prognostic clue in ischemic heart disease. *Clin Cardiol* 2004; **27:** 674–677. PMID: 15628108
38. Gerson MC, McHenry PL. Resting U wave inversion as a marker of stenosis of the left anterior descending coronary artery. *Am J Med* 1980; **69:** 545–550. PMID: 7424944
39. Bonoris PE, Greenberg PS, Christison GW, Castellanet MJ, Ellestad MH. Evaluation of R wave amplitude changes versus ST-segment depression in stress testing. *Circulation* 1978; **57:** 904–910. PMID: 639212
40. De Feyter PJ, Jong de JP, Roos JP, van Eenige MJ, de Jong JP. Diagnostic incapacity of exercise-induced QRS wave amplitude changes to detect coronary artery disease and left ventricular dysfunction. *Eur Heart J* 1982; **3:** 9–16. PMID: 7075616
41. Satomura K, Mizuno K, Shibuya T. Comparison of ST, R wave, and Q wave in exercise stress testing. *Electrocardiogram* 1985; **5:** 635–640 (in Japanese).
42. Nishimura Y, Yamakado T, Higashiyama S, Higashi Y, Kyo K, Nakano T, et al. Clinical significance of septal Q wave response on exercise testing in coronary artery disease. *Kokyu To Junkan* 1986; **34:** 999–1002 (in Japanese). PMID: 3786967
43. Whinnery JE, Froelicher VF Jr, Stewart AJ, Longo MR Jr, Triebwasser JH, Lancaster MC. The electrocardiographic response to maximal treadmill exercise of asymptomatic men with left bundle branch block. *Am Heart J* 1977; **94:** 316–324. PMID: 888764
44. Whinnery JE, Froelicher VF Jr, Longo MR Jr, Triebwasser JH. The electrocardiographic response to maximal treadmill exercise of asymptomatic men with right bundle branch block. *Chest* 1977; **71:** 335–340. PMID: 837747
45. Sundqvist K, Atterhög JH, Jogestrand T. Effect of digoxin on the electrocardiogram at rest and during exercise in healthy subjects. *Am J Cardiol* 1986; **57:** 661–665. PMID: 3953454
46. Kawakubo K, Ohta T, Musha H, Hashimoto T, Kaneko M, Sakai M, et al. A new computer-assisted automated diagnostic system (ML 1100) of exercise electrocardiography. *Jpn J Electrocardiogr* 1996; **16:** 369–375 (in Japanese). https://www.jstage.jst.go.jp/article/jse1981/16/4/16_4_369/_article/-char/ja/ (accessed Dec 25, 2019)
47. Hirakawa F, Chikamori T, Kitaoka Y, Matsumura Y, Takata J, Seo H, et al. Usefulness of dipiridamole thallium myocardial scintigraphy for the diagnosis of coronary artery disease in

elderly patients. *Nihon Ronen Igakkai Zasshi* 1997; **34:** 617–622. PMID: 9396316 (in Japanese). https://www.jstage.jst.go.jp/article/geriatrics1964/34/8/34_8_617/_article/-char/ja/ (accessed Dec 25, 2019).
48. Iwase M, Fukui M, Tamagaki H, Kimura M, Hasegawa K, Matsuyama H, et al. Advantages and disadvantages of dobutamine stress echocardiography compared with treadmill exercise electrocardiography in detecting ischemia. *Jpn Circ J* 1996; **60:** 954–960. PMID: 8996686
49. Yamagishi M, Aonuma K, Inoue H, Kimura T, Kubota I, Kuwahara Y, et al. JCS Working Group. Guidelines for diagnostic evaluation of patients with chronic ischemic heart disease (JCS 2010) (in Japanese). www.j-circ.or.jp/guideline/pdf/JCS2010_yamagishi_h.pdf (accessed Dec 25, 2019).
50. Crawford MH, Bernstein SJ, Deedwania PC, DiMarco JP, Ferrick KJ, Garson A Jr, et al. ACC/AHA Guidelines for Ambulatory Electrocardiography: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. *J Am Coll Cardiol* 1999; **34:** 912–948. PMID: 10483977
51. Sheffield LT, Berson A, Bragg-Remschel D, Gillette PC, Hermes RE, Hinkle L, et al. Recommendations for standards of instrumentation and practice in the use of ambulatory electrocardiography: The Task Force of the Committee on Electrocardiography and Cardiac Electrophysiology of the Council on Clinical Cardiology. *Circulation* 1985; **71:** 626A–636A. PMID: 3995702
52. Saito K, Otsuka K, Kubo Y, Murakami S. Holter electrocardiography: Structured basic knowledge and its new perspectives. Tokyo: Igakushuppansha, 2005; 111–126 (in Japanese).
53. Tzivoni D, Benhorin J, Gavish A, Stern S. Holter recording during treadmill testing in assessing myocardial ischemic changes. *Am J Cardiol* 1985; **55:** 1200–1203. PMID: 3984900
54. Tanabe T, Homma Y, Kanemoto N, Hinohara S, Goto Y. Studies on discrimination between ischemic and postural ST-T changes in ambulatory electrocardiographic monitoring. *Nihon Naika Gakkai Zasshi* 1984; **73:** 323–331 (in Japanese). PMID: 6736732 https://www.ncbi.nlm.nih.gov/pubmed/?term=6736732%5Buid%5D (accessed Dec 25, 2019).
55. Yanaga T, Ueno T, Ichimaru Y, Kodama Y, Yano K, Hata, Y, et al. Diagnosis of cardiac ischemia using Holter electrocardiography. *Jpn J Electrocardiology* 1986; **6:** 139–151 (in Japanese). https://www.jstage.jst.go.jp/article/jse1981/6/2/6_2_139/_article/-char/ja/ (accessed Dec 25, 2019).
56. Taddei A, Distante G, Emdin M, Pisani P, Moody GB, Zeelenberg C, et al. The European ST-T database: Standard for evaluating systems for the analysis of ST-T changes in ambulatory electrocardiography. *Eur Heart J* 1992; **13:** 1164–1172. PMID: 1396824
57. Crawford MH, Mendoza CA, O'Rourke RA, White DH, Boucher CA, Gorwit J. Limitations of continuous ambulatory electrocardiogram monitoring for detecting coronary artery disease. *Ann Intern Med* 1978; **89:** 1–5. PMID: 666154
58. Kadish AH, Buxton AE, Kennedy HL, Knight BP, Mason JW, Schuger CD, et al. ACC/AHA clinical competence statement on electrocardiography and ambulatory electrocardiography: A report of the ACC/AHA/ACP-ASIM task force on clinical competence (ACC/AHA Committee to develop a clinical competence statement on electrocardiography and ambulatory electrocardiography) endorsed by the International Society for Holter and noninvasive electrocardiology. *Circulation* 2001; **104:** 3169–3178. PMID: 11748119
59. The Committee of Japanese Society of Electrocardiology for Guideline Development of Holter Electrocardiography. The statement from Japanese Society of Electrocardiology on Holter electrocardiography. *Jpn J Electrocardiol* 2006; **26:** 871–937 (in Japanese). https://www.jstage.jst.go.jp/article/jse1981/26/6/26_6_871/_article/-char/ja/ (accessed Dec 25, 2019).
60. Steinberg JS, Varma N, Cygankiewicz I, Aziz P, Balsam P, Baranchuk A, et al. 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry. *Heart Rhythm* 2017; **14:** e55–e96. PMID: 28495301
61. Su L, Borov S, Zrenner B. 12-lead Holter electrocardiography. Review of the literature and clinical application update. *Herzschrittmacherther Elektrophysiol* 2013; **24:** 92–96. PMID: 23778563
62. Thompson RC1, Mackey DC, Lane GE, Blackshear JL, Shine TS, Ebener MK, et al. Improved detection of silent cardiac ischemia with a 12-lead portable microprocessor-driven real-time electrocardiographic monitor. *Mayo Clin Proc* 1995; **70:** 434–442. PMID: 7731252
63. Ogawa H, Akasaka T, Inoue T, Okumura K, Kawashima S, Kawasuji M, et al. Guidelines for diagnosis and treatment of patients with vasospactic angina (coronary spastic angina) (JCS2013) (in Japanese). http://www.j-circ.or.jp/guideline/pdf/JCS2013_ogawah_h.pdf (accessed Dec 25, 2019).
64. Conti CR, Bavry AA, Petersen JW. Silent ischemia: Clinical relevance. *J Am Coll Cardiol* 2012; **59:** 435–441. PMID: 22281245
65. Gottlieb SO, Gerstenblith G. Silent myocardial ischemia in the elderly: Current concepts. *Geriatrics* 1988; **43:** 29–34. PMID: 2965064
66. Fleg JL, Gerstenblith G, Zonderman AB, Becker LC, Weisfeldt ML, Costa PT Jr, et al. Prevalence and prognostic significance of exercise-induced silent myocardial ischemia detected by thallium scintigraphy and electrocardiography in asymptomatic volunteers. *Circulation* 1990; **81:** 428–436. PMID: 2297853
67. Ambepityia G1, Kopelman PG, Ingram D, Swash M, Mills PG, Timmis AD. Exertional myocardial ischemia in diabetes: A quantitative analysis of anginal perceptual threshold and the influence of autonomic function. *J Am Coll Cardiol* 1990; **15:** 72–77. PMID: 2295745
68. Naka M, Hiramatsu K, Aizawa T, Momose A, Yoshizawa K, Shigematsu S, et al. Silent myocardial ischemia in patients with non-insulin-dependent diabetes mellitus as judged by treadmill exercise testing and coronary angiography. *Am Heart J* 1992; **123:** 46–53. PMID: 1729850
69. Aronow WS, Mercando AD, Epstein S. Prevalence of silent myocardial ischemia detected by 24-hour ambulatory electrocardiography, and its association with new coronary events at 40-month follow-up in elderly diabetic and nondiabetic patients with coronary artery disease. *Am J Cardiol* 1992; **69:** 555–556. PMID: 1736624
70. Nakao YM, Ueshima K, Nohara R, Mizunuma Y, Segawa I, Tanaka-Mizuno S, et al. Holter monitoring for the screening of cardiac disease in diabetes mellitus: The non-invasive Holter monitoring observation of new cardiac events in diabetics study. *Diab Vasc Dis Res* 2015; **12:** 396–404. PMID: 26246490
71. Cohn PF. Silent myocardial ischemia: Classification, prevalence, and prognosis. *Am J Med* 1985; **79:** 2–6. PMID: 4050822
72. Quyyumi AA, Wright C, Fox K. Ambulatory electrocardiographic ST segment changes in healthy volunteers. *Br Heart J* 1983; **50:** 460–464. PMID: 6639817
73. Kohli RS, Cashman PM, Lahiri A, Raftery EB. The ST segment of the ambulatory electrocardiogram in a normal population. *Br Heart J* 1988; **60:** 4–16. PMID: 3408617
74. Giagnoni E, Secchi MB, Wu SC, Morabito A, Oltrona L, Mancarella S, et al. Prognostic value of exercise EKG testing in asymptomatic normotensive subjects: A prospective matched study. *N Engl J Med* 1983; **309:** 1085–1089. PMID: 6621650
75. Stern S, Gavish A, Weisz G, Benhorin J, Keren A, Tzivoni D. Characteristics of silent and symptomatic myocardial ischemia during daily activities. *Am J Cardiol* 1988; **61:** 1223–1228. PMID: 3376882
76. Kishida H, Saito T. Cardiac events in patients with silent myocardial ischemia. *Jpn Heart J* 1992; **33:** 1–13. PMID: 1573773
77. Kohya T, Tomita F, Itoh K, Suzuki Y, Kawabata N, Andoh J, et al. Silent myocardial ischemia during Holter monitoring in ischemic heart disease. *Jpn Circ J* 1989; **53:** 1399–1406. PMID: 2621769
78. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, et al; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: The DIAD study – a randomized controlled trial. *JAMA* 2009; **301:** 1547–1555. PMID: 19366774
79. American Diabetes Association. 9: Cardiovascular disease and risk management. *Diabetes Care* 2017; **40**(Suppl 1)**:** S75–S87. PMID: 27979896
80. Benhorin J, Banai S, Moriel M, Gavish A, Keren A, Stern S, et al. Circadian variations in ischemic threshold and their relation to the occurrence of ischemic episodes. *Circulation* 1993; **87:** 808–814. PMID: 8095188
81. Stone PH, Gibson RS, Glasser SP, DeWood MA, Parker JD, Kawanishi DT, et al. Comparison of propranolol, diltiazem, and nifedipine in the treatment of ambulatory ischemia in patients with stable angina. Differential effects on ambulatory ischemia, exercise performance, and anginal symptoms: The

ASIS study group. *Circulation* 1990; **82:** 1962–1972. PMID: 2122926
82. Braunwald E. Unstable angina: A classification. *Circulation* 1989; **80:** 410–414. PMID: 2752565
83. Quyyumi AA, Panza JA, Diodati JG, Lakatos E, Epstein SE. Circadian variation in ischemic threshold: A mechanism underlying the circadian variation in ischemic events. *Circulation* 1992; **86:** 22–28. PMID: 1617775
84. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. Heart rate variability from 24-hour electrocardiography and the 2-year risk for sudden death. *Circulation* 1993; **88:** 180–185. PMID: 8319331
85. Hayano J, Sakakibara Y, Yamada M, Ohte N, Fujinami T, Yokoyama K, et al. Decreased magnitude of heart rate spectral components in coronary artery disease: Its relation to angiographic severity. *Circulation* 1990; **81:** 1217–1224. PMID: 2317904
86. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. *Lancet* 1998; **351:** 478–484. PMID: 9482439
87. Gomes JA. The signal averaged ECG: A historical perspective. *In*: Gomes JA, editor. Signal averaged electrocardiography: Concepts, methods and applications. Dordecht, The Netherlands: Kluwer Academic Publishers, 1993; 3–10.
88. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol* 2006; **48:** e247–e346. PMID: 16949478
89. Aizawa Y, Horie M, Inoue H, Kamakura S, Katoh T, Matsuzaki M, et al. JCS Joint Working Group. Guidelines for risks and prevention of sudden cardiac death (JCS 2010): Digest version. *Circ J* 2012; **76:** 489–507. PMID: 22240604
90. Simson MB. Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction. *Circulation* 1981; **64:** 235–242. PMID: 7249291
91. Breithardt G, Borggrefe M. Recent advances in the identification of patients at risk of ventricular tachyarrhythmias: Role of ventricular late potentials. *Circulation* 1987; **75:** 1091–1096. PMID: 3552305
92. Kuchar DL, Thorburn CW, Sammel NL. Prediction of serious arrhythmic events after myocardial infarction: Signal-averaged electrocardiogram, Holter monitoring and radionuclide ventriculography. *J Am Coll Cardiol* 1987; **9:** 531–538. PMID: 3819200
93. Gomes JA, Winters SL, Stewart D, Horowitz S, Milner M, Barreca P. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction: Based on signal-averaged electrocardiogram, radionuclide ejection fraction and Holter monitoring. *J Am Coll Cardiol* 1987; **10:** 349–357. PMID: 3598005
94. Ikeda T, Sakata T, Takami M, Kondo N, Tezuka N, Nakae T, et al. Combined assessment of T-wave alternans and late potentials used to predict arrhythmic events after myocardial infarction: A prospective study. *J Am Coll Cardiol* 2000; **35:** 722–730. PMID: 10716476
95. Bigger JT. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med* 1997; **337:** 1569–1575. PMID: 9371853
96. Rosenbaum DS, Jackson LE, Smith JM, Garan H, Ruskin JN, Cohen RJ. Electrical alternans and vulnerability to ventricular arrhythmias. *N Engl J Med* 1994; **330:** 235–241. PMID: 8272084
97. Ikeda T, Yoshino H, Sugi K, Tanno K, Shimizu H, Watanabe J, et al. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: Results of a collaborative cohort study. *J Am Coll Cardiol* 2006; **48:** 2268–2274. PMID: 17161258
98. Ikeda T, Saito H, Tanno K, Shimizu H, Watanabe J, Ohnishi Y, et al. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. *Am J Cardiol* 2002; **89:** 79–82. PMID: 11779531
99. Hohnloser SH, Ikeda T, Bloomfield DM, Dabbous OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. *Lancet* 2003; **362:** 125–126. PMID: 12867114
100. Bloomfield DM, Steinman RC, Namerow PB, Parides M, Davidenko J, Kaufman ES, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: A solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. *Circulation* 2004; **110:** 1885–1889. PMID: 15451804
101. Chow T, Kereiakes DJ, Onufer J, Woelfel A, Gursoy S, Peterson BJ, et al. MASTER Trial Investigators. Does microvolt T-wave alternans testing predict ventricular tachyarrhythmias in patients with ischemic cardiomyopathy and prophylactic defibrillators? The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post-Myocardial Infarction Patients) trial. *J Am Coll Cardiol* 2008; **52:** 1607–1615. PMID: 18992649
102. Costantini O, Hohnloser SH, Kirk MM, Lerman BB, Baker JH 2nd, Sethuraman B, et al. ABCD Trial Investigators. The ABCD (Alternans Before Cardioverter Defibrillator) Trial: Strategies using T-wave alternans to improve efficiency of sudden cardiac death prevention. *J Am Coll Cardiol* 2009; **53:** 471–479. PMID: 19195603
103. Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH, et al. Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility: Consensus guideline by International Society for Holter and Noninvasive Electrocardiology. *J Am Coll Cardiol* 2011; **58:** 1309–1324. PMID: 21920259
104. Watanabe T, Toyama J, Toyoshima H, Oguri H, Ohno M, Ohta T, Okajima M, et al. A practical microcomputer-based mapping system for body surface, precordium, and epicardium. *Comput Biomed Res* 1981; **14:** 341–354. PMID: 7261573
105. Hirai M, Ohta T, Kinoshita A, Toyama J, Nagaya T, Yamada K. Body surface isopotential maps in old anterior myocardial infarction undetectable by 12-lead electrocardiograms. *Am Heart J* 1984; **108:** 975–982. PMID: 6486010
106. Yamaki M, Ikeda K, Honma K, Kiriyama N, Tono-oka I, Tsuiki K, et al. Diagnosis of right ventricular involvement in chronic inferior myocardial infarction by means of body surface QRS changes. *Circulation* 1988; **77:** 1283–1290. PMID: 3370768
107. Ishikawa T, Watabe S, Yamada Y, Miyachi K, Sakai Y, Ito A, et al. New diagnostic evidence on the T wave map indicating involved coronary artery in patients with angina pectoris. *Circulation* 1988; **77:** 301–310. PMID: 3338127
108. Kubota I, Hanashima K, Ikeda K, Tsuiki K, Yasui S. Detection of diseased coronary artery by exercise ST-T maps in patients with effort angina pectoris, single-vessel disease, and normal ST-T wave on electrocardiogram at rest. *Circulation* 1989; **80:** 120–127. PMID: 2736744
109. Tonooka I, Kubota I, Watanabe Y, Tsuiki K, Yasui S. Isointegral analysis of body surface maps for the assessment of location and size of myocardial infarction. *Am J Cardiol* 1983; **52:** 1174–1180. PMID: 6650405
110. Kubota I, Ikeda K, Kanaya T, Yamaki M, Tonooka I, Watanabe Y, et al. Noninvasive assessment of left ventricular wall motion abnormalities by QRS isointegral maps in previous anterior infarction. *Am Heart J* 1985; **109:** 464–471. PMID: 3976471
111. Nakajima T, Kawakubo K, Toda I, Mashima S, Ohtake T, Iio M, et al. ST-T isointegral analysis of exercise stress body surface mapping for identifying ischemic areas in patients with angina pectoris. *Am Heart J* 1988; **115:** 1013–1021. PMID: 3364334
112. Gardner MJ, Montague TJ, Armstrong CS, Horacek BM, Smith ER. Vulnerability to ventricular arrhythmia: Assessment by mapping of body surface potential. *Circulation* 1986; **73:** 684–692. PMID: 3948371
113. Igarashi H, Yamaki M, Kubota I, Ikeda K, Matsui M, Tsuiki K, et al. Relation between localization of coronary artery disease and local abnormalities in ventricular activation during exercise tests. *Circulation* 1990; **81:** 461–469. PMID: 2297856
114. Baule G, McFee R. Detection of the magnetic field of the heart. *Am Heart J* 1963; **66:** 95–96. PMID: 14045992
115. Cohen D, Kaufman LA. Magnetic determination of the relationship between the S-T segment shift and the injury current

produced by coronary artery occlusion. *Circ Res* 1975; **36:** 414–424. PMID: 1111998
116. Weismüller P, Abraham-Fuchs K, Killmann R, Richter P, Härer W, Höher M, et al. Magnetocardiography: Three-dimensional localization of the origin of ventricular late fields in the signal averaged magnetocardiogram in patients with ventricular late potentials. *Eur Heart J* 1993; **14**(Suppl)**:** 61–68. PMID: 8223757
117. Nomura M, Nakaya Y, Fujino K, Ishihara S, Katayama M, Takeuchi A, et al. Magnetocardiographic studies of ventricular repolarization in old inferior myocardial infarction. *Eur Heart J* 1989; **10:** 8–15. PMID: 2702969
118. Tsukada K, Miyashita T, Kandori A, Mitsui T, Terada Y, Sato M, et al. An iso-integral mapping technique using magnetocardiogram, and its possible use for diagnosis of ischemic heart disease. *Int J Card Imaging* 2000; **16:** 55–66. PMID: 10832626
119. On K, Watanabe S, Yamada S, Takeyasu N, Nakagawa Y, Nishina H, et al. Integral value of JT interval in magnetocardiography is sensitive to coronary stenosis and improves soon after coronary revascularization. *Circ J* 2007; **71:** 1586–1592. PMID: 17895556
120. Kanzaki H, Nakatani S, Kandori A, Tsukada K, Miyatake K. A new screening method to diagnose coronary artery disease using multichannel magnetocardiogram and simple exercise. *Basic Res Cardiol* 2003; **98:** 124–132. PMID: 12607134
121. Daly C, Norrie J, Murdoch DL, Ford I, Dargie HJ, Fox K; TIBET (Total Ischaemic Burden European Trial) study group. The value of routine non-invasive tests to predict clinical outcome in stable angina. *Eur Heart J* 2003; **24:** 532–540. PMID: 12643886
122. Daly CA, De Stavola B, Sendon JL, Tavazzi L, Boersma E, Clemens F, et al; Euro Heart Survey Investigators. Predicting prognosis in stable angina: Results from the Euro heart survey of stable angina – prospective observational study. *BMJ* 2006; **332:** 262–267. PMID: 16415069
123. Eitel I, de Waha S, Wöhrle J, Fuernau G, Lurz P, Pauschinger M, et al. Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2014; **64:** 1217–1226. PMID: 25236513
124. Vitarelli A1, Tiukinhoy S, Di Luzio S, Zampino M, Gheorghiade M. The role of echocardiography in the diagnosis and management of heart failure. *Heart Fail Rev* 2003; **8:** 181–189. PMID: 12766498
125. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014; **64:** 1929–1949. PMID: 25077860
126. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012; **60:** e44–e164. PMID: 23182125
127. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the Management of Stable Coronary Artery Disease of the European Society of Cardiology. *Eur Heart J* 2013; **34:** 2949–3003. PMID: 23996286
128. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. *J Am Coll Cardiol* 2011; **57:** 1126–1166. PMID: 21349406
129. Gibbons RJ, Carryer D, Liu H, Brady PA, Askew JW, Hodge D, et al. Use of echocardiography in outpatients with chest pain and normal resting electrocardiograms referred to Mayo Clinic Rochester. *Am Heart J* 2018; **196:** 49–55. PMID: 29421014
130. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: Consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16:** 1–11. PMID: 25525063
131. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28:** 1–39.e14. PMID: 25559473
132. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002; **105:** 539–542. PMID: 11815441
133. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; **29:** 277–314. PMID: 27037982
134. Hozumi T, Yoshida K, Akasaka T, Asami Y, Ogata Y, Takagi T, et al. Noninvasive assessment of coronary flow velocity and coronary flow velocity reserve in the left anterior descending coronary artery by Doppler echocardiography: Comparison with invasive technique. *J Am Coll Cardiol* 1998; **32:** 1251–1259. PMID: 9809933
135. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ, et al. Ischemic mitral regurgitation: Long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001; **103:** 1759–1764. PMID: 11282907
136. Wada Y, Ohara T, Funada A, Hasegawa T, Sugano Y, Kanzaki, et al. Prognostic impact of functional mitral regurgitation in patients admitted with acute decompensated heart failure. *Circ J* 2016; **80:** 139–147. PMID: 26558879
137. Abdelmoneim SS, Bernier M, Dhoble A, Moir S, Hagen ME, Ness SA, et al. Assessment of myocardial perfusion during adenosine stress using real time three-dimensional and two-dimensional myocardial contrast echocardiography: Comparison with single-photon emission computed tomography. *Echocardiography* 2010; **27:** 421–429. PMID: 20331695
138. Voigt JU, Exner B, Schmiedehausen K, Huchzermeyer C, Reulbach U, Nixdorff U, et al. Strain-rate imaging during dobutamine stress echocardiography provides objective evidence of inducible ischemia. *Circulation* 2003; **107:** 2120–2126. PMID: 12682001
139. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004; **17:** 1021–1029. PMID: 15452466
140. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *J Am Soc Echocardiogr* 2011; **24:** 277–313. PMID: 21338865
141. Armstrong WF, O'Donnell J, Dillon JC, McHenry PL, Morris SN, Feigenbaum H, et al. Complementary value of two-dimensional exercise echocardiography to routine treadmill exercise testing. *Ann Intern Med* 1986; **105:** 829–835. PMID: 3777710
142. Hecht HS, DeBord L, Shaw R, Dunlap R, Ryan C, Stertzer SH, et al. Digital supine bicycle stress echocardiography: A new technique for evaluating coronary artery disease. *J Am Coll Cardiol* 1993; **21:** 950–956. PMID: 8450164
143. Picano E. Stress echocardiography: From pathophysiological

toy to diagnostic tool. *Circulation* 1992; **85:** 1604–1612. PMID: 1555297
144. Takeuchi M, Araki M, Nakashima Y, Kuroiwa A. Comparison of dobutamine stress echocardiography and stress thallium-201 single-photon emission computed tomography for detecting coronary artery disease. *J Am Soc Echocardiogr* 1993; **6:** 593–602. PMID: 8311966
145. Cigarroa CG, deFilippi CR, Brickner ME, Alvarez LG, Wait MA, Grayburn PA, et al. Dobutamine stress echocardiography identifies hibernating myocardium and predicts recovery of left ventricular function after coronary revascularization. *Circulation* 1993; **88:** 430–436. PMID: 8339406
146. Afridi I, Kleiman NS, Raizner AE, Zoghbi WA. Dobutamine echocardiography in myocardial hibernation. Optimal dose and accuracy in predicting recovery of ventricular function after coronary angioplasty. *Circulation* 1995; **91:** 663–670. PMID: 7828291
147. Perrone-Filardi P, Pace L, Prastaro M, Piscione F, Betocchi S, Squame F, et al. Dobutamine echocardiography predicts improvement of hypoperfused dysfunctional myocardium after revascularization in patients with coronary artery disease. *Circulation* 1995; **91:** 2556–2565. PMID: 7743617
148. Galanti G, Sciagrà R, Comeglio M, Taddei T, Bonechi F, Giusti F, et al. Diagnostic accuracy of peak exercise echocardiography in coronary artery disease: Comparison with thallium-201 myocardial scintigraphy. *Am Heart J* 1991; **122:** 1609–1616. PMID: 1957756
149. Ryan T, Vasey CG, Presti CF, O'Donnell JA, Feigenbaum H, Armstrong WF, et al. Exercise echocardiography: Detection of coronary artery disease in patients with normal left ventricular wall motion at rest. *J Am Coll Cardiol* 1988; **11:** 993–999. PMID: 3356843
150. Armstrong WF, O'Donnell J, Ryan T, Feigenbaum H. Effect of prior myocardial infarction and extent and location of coronary disease on accuracy of exercise echocardiography. *J Am Coll Cardiol* 1987; **10:** 531–538. PMID: 3624660
151. Hozumi T, Yoshida K, Ogata Y, Akasaka T, Asami Y, Takagi T, et al. Noninvasive assessment of significant left anterior descending coronary artery stenosis by coronary flow velocity reserve with transthoracic color Doppler echocardiography. *Circulation* 1998; **97:** 1557–1562. PMID: 9593560
152. Ellis SG, Wynne J, Braunwald E, Henschke CI, Sandor T, Kloner RA, et al. Response of reperfusion-salvaged, stunned myocardium to inotropic stimulation. *Am Heart J* 1984; **107:** 13–19. PMID: 6691220
153. Piérard LA, De Landsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: Comparison with positron emission tomography. *J Am Coll Cardiol* 1990; **15:** 1021–1031. PMID: 2312956
154. Previtali M, Poli A, Lanzarini L, Fetiveau R, Mussini A, Ferrario M, et al. Dobutamine stress echocardiography for assessment of myocardial viability and ischemia in acute myocardial infarction treated with thrombolysis. *Am J Cardiol* 1993; **72:** G124–G130. PMID: 8279348
155. Hoffmann R, Altiok E, Nowak B, Heussen N, Kühl H, Kaiser HJ, et al. Strain rate measurement by doppler echocardiography allows improved assessment of myocardial viability inpatients with depressed left ventricular function. *J Am Coll Cardiol* 2002; **39:** 443–449. PMID: 11823082
156. Dilsizian V, Bonow RO. Current diagnostic techniques of assessing myocardial viability in patients with hibernating and stunned myocardium. *Circulation* 1993; **87:** 1–20. PMID: 8418996
157. Schulz R, Guth BD, Pieper K, Martin C, Heusch G. Recruitment of an inotropic reserve in moderately ischemic myocardium at the expense of metabolic recovery: A model of short-term hibernation. *Circ Res* 1992; **70:** 1282–1295. PMID: 1576742
158. La Canna G, Alfieri O, Giubbini R, Gargano M, Ferrari R, Visioli O, et al. Echocardiography during infusion of dobutamine for identification of reversibly dysfunction in patients with chronic coronary artery disease. *J Am Coll Cardiol* 1994; **23:** 617–626. PMID: 8113543
159. Sawada SG, Ryan T, Conley MJ, Corya BC, Feigenbaum H, Armstrong WF, et al. Prognostic value of a normal exercise echocardiogram. *Am Heart J* 1990; **120:** 49–55. PMID: 2360517
160. Afridi I, Quiñones MA, Zoghbi WA, Cheirif J, et al. Dobutamine stress echocardiography: Sensitivity, specificity, and predictive value for future cardiac events. *Am Heart J* 1994; **127:** 1510–1515. PMID: 8197976
161. Krivokapich J, Child JS, Gerber RS, Lem V, Moser D. Prognostic usefulness of positive or negative exercise stress echocardiography for predicting coronary events in ensuing twelve months. *Am J Cardiol* 1993; **71:** 646–651. PMID: 8447259
162. Williams MJ, Odabashian J, Lauer MS, Thomas JD, Marwick TH. Prognostic value of dobutamine echocardiography in patients with left ventricular dysfunction. *J Am Coll Cardiol* 1996; **27:** 132–139. PMID: 8522686
163. Kamaran M, Teague SM, Finkelhor RS, Dawson N, Bahler RC. Prognostic value of dobutamine stress echocardiography in patients referred because of suspected coronary artery disease. *Am J Cardiol* 1995; **76:** 887–891. PMID: 7484826
164. Marcovitz PA, Shayna V, Horn RA, Hepner A, Armstrong WF. Value of dobutamine stress echocardiography in determining the prognosis of patients with known or suspected coronary artery disease. *Am J Cardiol* 1996; **78:** 404–408. PMID: 8752183
165. Christie J, Sheldahl LM, Tristani FE, Sagar KB, Ptacin MJ, Wann S. Determination of stroke volume and cardiac output during exercise: Comparison of two-dimensional and Doppler echocardiography, Fick oximetry, and thermodilution. *Circulation* 1987; **76:** 539–547. PMID: 3621519
166. Iwase M, Yokota M, Maeda M, Kamihara S, Miyahara T, Iwase M, et al. Noninvasive detection of exercise-induced markedly elevated left ventricular filling pressure by pulsed Doppler echocardiography in patients with coronary artery disease. *Am Heart J* 1989; **118:** 947–954. PMID: 2816706
167. Labovitz AJ, Pearson AC, Chaitman BR. Doppler and two-dimensional echocardiographic assessment of left ventricular function before and after intravenous dipyridamole stress testing for detection of coronary artery disease. *Am J Cardiol* 1988; **62:** 1180–1185. PMID: 3195479
168. Maeda M, Yokota M, Iwase M, Miyahara T, Hayashi H, Sotobata I. Accuracy of cardiac output measured by continuous wave Doppler echocardiography during dynamic exercise testing in the supine position in patients with coronary artery disease. *J Am Coll Cardiol* 1989; **13:** 76–83. PMID: 2909584
169. Beleslin BD, Ostojic M, Stepanovic J, Djordjevic-Dikic A, Stojkovic S, Nedeljkovic M, et al. Stress echocardiography in the detection of myocardial ischemia: Head-to-head comparison of exercise, dobutamine, and dipyridamole tests. *Circulation* 1994; **90:** 1168–1176. PMID: 7916274
170. Fung AY, Gallagher KP, Buda AJ. The physiologic basis of dobutamine as compared with dipyridamole stress interventions in the assessment of critical coronary stenosis. *Circulation* 1987; **76:** 943–951. PMID: 3652428
171. Koyanagi S, Honma H. *In*: Takano T, editor. Stress echocardiography. Tokyo: Nakayama-shoten, 1997; 25 (in Japanese).
172. Yoshitani H, Takeuchi M, Mor-Avi V, Otsuji Y, Hozumi T, Yoshiyama M. Comparative diagnostic accuracy of multiplane and multislice three-dimensional dobutamine stress echocardiography in the diagnosis of coronary artery disease. *J Am Soc Echocardiogr* 2009; **22:** 437–442. PMID: 19307099
173. Joyce E, Hoogslag GE, Al Amri I, Debonnaire P, Katsanos S, Bax JJ, et al. Quantitative dobutamine stress echocardiography using speckle-tracking analysis versus conventional visual analysis for detection of significant coronary artery disease after ST-segment elevation myocardial infarction. *J Am Soc Echocardiogr* 2015; **28:** 1379–1389.e1. PMID: 26307373
174. Ng AC, Sitges M, Pham PN, Tran da T, Delgado V, Bertini M, et al. Incremental value of 2-dimensional speckle tracking strain imaging to wall motion analysis for detection of coronary artery disease in patients undergoing dobutamine stress echocardiography. *Am Heart J* 2009; **158:** 836–844. PMID: 19853706
175. Yang LT, Kado Y, Nagata Y, Otani K, Otsuji Y, Takeuchi M. Strain imaging with a Bull's-Eye map for detecting significant coronary stenosis during dobutamine stress echocardiography. *J Am Soc Echocardiogr* 2017; **30:** 159–167.e1. PMID: 27916236
176. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: Validation against sonomicrometry and tagged magnetic resonance imaging. *J Am Coll Cardiol* 2006; **47:** 789–793. PMID: 16487846
177. Seo Y, Ishizu T, Enomoto Y, Sugimori H, Yamamoto M, Machino T, Kawamura R, et al. Validation of 3-dimensional speckle tracking imaging to quantify regional myocardial deformation. *Circ Cardiovasc Imaging* 2009; **2:** 451–459. PMID: 19920043
178. Farsalinos KE, Daraban AM, Ünlü S, Thomas JD, Badano LP,

Voigt JU, et al. Head-to-head comparison of global longitudinal strain measurements among nine different vendors: The EACVI/ase inter-vendor comparison study. *J Am Soc Echocardiogr* 2015; **28:** 1171–1181.e2. PMID: 26209911
179. Gjesdal O, Helle-Valle T, Hopp E, Lunde K, Vartdal T, Aakhus S, et al. Noninvasive separation of large, medium, and small myocardial infarcts in survivors of reperfused ST-elevation myocardial infarction: A comprehensive tissue Doppler and speckle-tracking echocardiography study. *Circ Cardiovasc Imaging* 2008; **1:** 189–196. PMID: 19808542
180. Mollema SA, Delgado V, Bertini M, Antoni ML, Boersma E, Holman ER, et al. Viability assessment with global left ventricular longitudinal strain predicts recovery of left ventricular function after acute myocardial infarction. *Circ Cardiovasc Imaging* 2010; **3:** 15–23. PMID: 19820202
181. Antoni ML, Mollema SA, Delgado V, Atary JZ, Borleffs CJ, Boersma E, et al. Prognostic importance of strain and strain rate after acute myocardial infarction. *Eur Heart J* 2010; **31:** 1640–1647. PMID: 20423918
182. Ersbøll M, Valeur N, Mogensen UM, Andersen MJ, Møller JE, Velazquez EJ, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2013; **61:** 2365–2373. PMID: 23563128
183. Bertini M, Ng AC, Antoni ML, Nucifora G, Ewe SH, Auger D, et al. Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy. *Circ Cardiovasc Imaging* 2012; **5:** 383–391. PMID: 22412068
184. Nahum J, Bensaid A, Dussault C, Macron L, Clémence D, Bouhemad B, et al. Impact of longitudinal myocardial deformation on the prognosis of chronic heart failure patients. *Circ Cardiovasc Imaging* 2010; **3:** 249–256. PMID: 20233858
185. Mignot A, Donal E, Zaroui A, Reant P, Salem A, Hamon C, et al. Global longitudinal strain as a major predictor of cardiac events in patients with depressed left ventricular function: A multicenter study. *J Am Soc Echocardiogr* 2010; **23:** 1019–1024. PMID: 20810243
186. Sengeløv M, Jørgensen PG, Jensen JS, Bruun NE, Olsen FJ, Fritz-Hansen, et al. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. *JACC Cardiovasc Imaging* 2015; **8:** 1351–1359. PMID: 26577264
187. Haugaa KH1, Grenne BL, Eek CH, Ersbøll M, Valeur N, Svendsen JH, et al. Strain echocardiography improves risk prediction of ventricular arrhythmias after myocardial infarction. *JACC Cardiovasc Imaging* 2013; **6:** 841–850. PMID: 23850251
188. Weidemann F, Dommke C, Bijnens B, Claus P, D'hooge J, Mertens P, et al. Defining the transmurality of a chronic myocardial infarction by ultrasonic strain-rate imaging: Implications for identifying intramural viability: An experimental study. *Circulation* 2003; **107:** 883–888. PMID: 12591760
189. Becker M, Ocklenburg C, Altiok E, Füting A, Balzer J, Krombach G, et al. Impact of infarct transmurality on layer-specific impairment of myocardial function: A myocardial deformation imaging study. *Eur Heart J* 2009; **30:** 1467–1476. PMID: 19351689
190. Mirea O, Pagourelias ED, Duchenne J, Bogaert J, Thomas JD, Badano LP, et al. Variability and reproducibility of segmental longitudinal strain measurement: A report from the EACVI-ASE strain standardization task force. *JACC Cardiovasc Imaging* 2018; **11:** 15–24. PMID: 28528147
191. Lim YJ, Nanto S, Masuyama T, Kodama K, Ikeda T, Kitabatake A, et al. Visualization of subendocardial myocardial ischemia with myocardial contrast echocardiography in humans. *Circulation* 1989; **79:** 233–244. PMID: 2914344
192. Kaul S, Senior R, Dittrich H, Raval U, Khattar R, Lahiri A. Detection of coronary artery disease with myocardial contrast echocardiography: Comparison with $^{99m}$Tc-sestamibi single-photon emission computed tomography. *Circulation* 1997; **96:** 785–792. PMID: 9264483
193. Wei K, Crouse L, Weiss J, Villanueva F, Schiller NB, Naqvi TZ, et al. Comparison of usefulness of dipyridamole stress myocardial contrast echocardiography to technetium-99 m sestamibi single-photon emission computed tomography for detection of coronary artery disease (PB127 Multicenter Phase 2 Trial results). *Am J Cardiol* 2003; **91:** 1293–1298. PMID: 12767419
194. Porter TR, Xie F, Silver M, Kricsfeld D, Oleary E. Real-time perfusion imaging with low mechanical index pulse inversion Doppler imaging. *J Am Coll Cardiol* 2001; **37:** 748–753. PMID: 11693747
195. Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. *Circulation* 1998; **97:** 473–483. PMID: 9490243
196. Masugata H, Lafitte S, Peters B, Strachan GM, DeMaria AN. Comparison of real-time and intermittent triggered myocardial contrast echocardiography for quantification of coronary stenosis severity and transmural perfusion gradient. *Circulation* 2001; **104:** 1550–1556. PMID: 11571251
197. Wei K, Ragosta M, Thorpe J, Coggins M, Moos S, Kaul S. Noninvasive quantification of coronary blood flow reserve in humans using myocardial contrast echocardiography. *Circulation* 2001; **103:** 2560–2565. PMID: 11382724
198. Ito H, Tomooka T, Sakai N, Yu H, Higashino Y, Fujii K, et al. Lack of myocardial perfusion immediately after successful thrombolysis: A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation* 1992; **85:** 1699–1705. PMID: 1572028
199. Asanuma T, Tanabe K, Ochiai K, Yoshitomi H, Nakamura K, Murakami Y. Relationship between progressive microvascular damage and intramyocardial hemorrhage in patients with reperfused anterior myocardial infarction: Myocardial contrast echocardiographic study. *Circulation* 1997; **96:** 448–453. PMID: 9244211
200. Bolognese L, Carrabba N, Parodi G, Santoro GM, Buonamici P, Cerisano G, et al. Impact of microvascular dysfunction on left ventricular remodeling and long-term clinical outcome after primary coronary angioplasty for acute myocardial infarction. *Circulation* 2004; **109:** 1121–1126. PMID: 14967718
201. Shimoni S, Frangogiannis NG, Aggeli CJ, Shan K, Verani MS, Quinones MA, et al. Identification of hibernating myocardium with quantitative intravenous myocardial contrast echocardiography: Comparison with dobutamine echocardiography and thallium-201 scintigraphy. *Circulation* 2003; **107:** 538–544. PMID: 12566363
202. Kaufmann PA, Di Carli MF. Hybrid SPECT/CT and PET/CT imaging: The next step in noninvasive cardiac imaging. *Semin Nucl Med* 2009; **39:** 341–347. PMID: 19646558
203. Gaemperli O, Saraste A, Knuuti J. Cardiac hybrid imaging. *Eur Heart J Cardiovasc Imaging* 2012; **13:** 51–60. PMID: 22094239
204. Pazhenkottil AP, Nkoulou RN, Ghadri JR, Herzog BA, Küest SM, Husmann L, et al. Impact of cardiac hybrid single-photon emission computed tomography/computed tomography imaging on choice of treatment strategy in coronary artery disease. *Eur Heart J* 2011; **32:** 2824–2829. PMID: 21804107
205. Heijenbrok-Kal MH, Fleischmann KE, Hunink MG. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: A meta-analysis of diagnostic performance. *Am Heart J* 2007; **154:** 415–423. PMID: 17719283
206. Higgins JP, Williams G, Nagel JS, Higgins JA. Left bundle-branch block artifact on single photon emission computed tomography with technetium Tc 99 m (Tc-99 m) agents: Mechanisms and a method to decrease false-positive interpretations. *Am Heart J* 2006; **152:** 619–626. PMID: 16996825
207. Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, et al; British Cardiac Society. Myocardial perfusion scintigraphy: The evidence. A consensus conference organised by the British Cardiac Society, the British Nuclear Cardiology Society and the British Nuclear Medicine Society, endorsed by the Royal College of Physicians of London and the Royal College of Radiologists. *Eur J Nucl Med Mol Imaging* 2004; **31:** 261–291. PMID: 15129710
208. Underwood SR, Shaw LJ, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint J, et al. Myocardial perfusion scintigraphy and cost effectiveness of diagnosis and management of coronary heart disease. *Heart* 2004; **90**(Suppl)**:** v34–v36. PMID: 15254007
209. Marcassa C, Bax JJ, Bengel F, Hesse B, Petersen CL, Reyes E, et al; European Council of Nuclear Cardiology (ECNC), European Society of Cardiology Working Group 5 (Nuclear Cardiology and Cardiac CT), European Association of Nuclear Medicine Cardiovascular Committee. Clinical value, cost-effectiveness, and safety of myocardial perfusion scintigraphy: A position statement. *Eur Heart J* 2008; **29:** 557–563. PMID: 18202253
210. Elhendy A, Schinkel AF, Bax JJ, van Domburg RT, Valkema

R, Biagini E, et al. Accuracy of stress Tc-99m tetrofosmin myocardial perfusion tomography for the diagnosis and localization of coronary artery disease in women. *J Nucl Cardiol* 2006; **13:** 629–634. PMID: 16945742
211. Shaw LJ, Mieres JH, Hendel RH, Boden WE, Gulati M, Veledar E, et al; WOMEN Trial Investigators. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: Results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation* 2011; **124:** 1239–1249. PMID: 21844080
212. Sabharwal NK, Stoykova B, Taneja AK, Lahiri A. A randomized trial of exercise treadmill ECG versus stress SPECT myocardial perfusion imaging as an initial diagnostic strategy in stable patients with chest pain and suspected CAD: Cost analysis. *J Nucl Cardiol* 2007; **14:** 174–186. PMID: 17386379
213. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA* 1998; **280:** 913–920. PMID: 9739977
214. Makita A, Matsumoto N, Suzuki Y, Hori Y, Kuronuma K, Yoda S, et al. Clinical feasibility of simultaneous acquisition rest $^{99m}$Tc/stress $^{201}$Tl dual-Isotope myocardial perfusion single-photon emission computed tomography with semiconductor camera. *Circ J* 2016; **80:** 689–695. PMID: 26781361
215. Chikamori T, Goto K, Hida S, Miyagawa M, Ishimura H, Uchida K, et al. Diagnostic performance of a semiconductor gamma-camera system as studied by multicenter registry. *J Cardiol* 2017; **69:** 449–455. PMID: 27021428
216. Gimelli A, Liga R, Duce V, Kusch A, Clemente A, Marzullo P. Accuracy of myocardial perfusion imaging in detecting multivessel coronary artery disease: A cardiac CZT study. *J Nucl Cardiol* 2017; **24:** 687–695. PMID: 26846367
217. Matsumoto N, Sato Y, Suzuki Y, Kasama S, Nakano Y, Kato M, et al. Incremental prognostic value of cardiac function assessed by ECG-gated myocardial perfusion SPECT for the prediction of future acute coronary syndrome. *Circ J* 2008; **72:** 2035–2039. PMID: 18948667
218. Berman DS, Kang X, Slomka PJ, Gerlach J, de Yang L, Hayes SW, et al. Underestimation of extent of ischemia by gated SPECT myocardial perfusion imaging in patients with left main coronary artery disease. *J Nucl Cardiol* 2007; **14:** 521–528. PMID: 17679060
219. Fukushima K, Javadi MS, Higuchi T, Lautamäki R, Merrill J, Nekolla SG, et al. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical $^{82}$Rb PET perfusion imaging. *J Nucl Med* 2011; **52:** 726–732. PMID: 21498538
220. El Fakhri G, Kardan A, Sitek A, Dorbala S, Abi-Hatem N, Lahoud Y, et al. Reproducibility and accuracy of quantitative myocardial blood flow assessment with $^{82}$Rb PET: Comparison with $^{13}$N-ammonia PET. *J Nucl Med* 2009; **50:** 1062–1071. PMID: 19525467
221. van der Veen BJ, Kuperij N, Stokkel MP. Transient ischemic dilatation ratio derived from myocardial perfusion scintigraphy: What are we looking at? *J Nucl Cardiol* 2010; **17:** 207–215. PMID: 20035391
222. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: A meta-analysis. *J Am Coll Cardiol* 2007; **49:** 227–237. PMID: 17222734
223. Nishimura T, Nakajima K, Kusuoka H, Yamashina A, Nishimura S. Prognostic study of risk stratification among Japanese patients with ischemic heart disease using gated myocardial perfusion SPECT: J-ACCESS study. *Eur J Nucl Med Mol Imaging* 2008; **35:** 319–328. PMID: 17926033
224. Hachamovitch R, Rozanski A, Shaw LJ, Stone GW, Thomson LE, Friedman JD, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011; **32:** 1012–1024. PMID: 21258084
225. Hachamovitch R, Rozanski A, Hayes SW, Thomson LE, Germano G, Friedman JD, et al. Predicting therapeutic benefit from myocardial revascularization procedures: Are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? *J Nucl Cardiol* 2006; **13:** 768–778. PMID: 17174808
226. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: Results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation* 2008; **117:** 1283–1291. PMID: 18268144
227. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; **107:** 2900–2907. PMID: 12771008
228. Allman KC. Noninvasive assessment myocardial viability: Current status and future directions. *J Nucl Cardiol* 2013; **20:** 618–637. PMID: 23771636
229. Bax JJ, van der Wall EE, Harbinson M. Radionuclide techniques for the assessment of myocardial viability and hibernation. *Heart* 2004; **90**(Suppl)**:** v26–v33. PMID: 15254006
230. Bax JJ, Wijns W, Cornel JH, Visser FC, Boersma E, Fioretti PM. Accuracy of currently available techniques for prediction of functional recovery after revascularization in patients with left ventricular dysfunction due to chronic coronary artery disease: Comparison of pooled data. *J Am Coll Cardiol* 1997; **30:** 1451–1460. PMID: 9362401
231. Patel P, Ivanov A, Ramasubbu K. Myocardial viability and revascularization: Current understanding and future directions. *Curr Atheroscler Rep* 2016; **18:** 32. PMID: 27115143
232. Bax JJ, Poldermans D, Elhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. *Curr Probl Cardiol* 2001; **26:** 147–186. PMID: 11276916
233. Sciagrà R, Bisi G, Santoro GM, Zerauschek F, Sestini S, Pedenovi P, et al. Comparison of baseline-nitrate technetium-99m sestamibi with rest-redistribution thallium-201 tomography in detecting viable hibernating myocardium and predicting postrevascularization recovery. *J Am Coll Cardiol* 1997; **30:** 384–391. PMID: 9247509
234. Udelson JE, Coleman PS, Metherall J, Pandian NG, Gomez AR, Griffith JL, et al. Predicting recovery of severe regional ventricular dysfunction. Comparison of resting scintigraphy with $^{201}$Tl and $^{99m}$Tc-sestamibi. *Circulation* 1994; **89:** 2552–2561. PMID: 8205664
235. Einstein AJ, Pascual TN, Mercuri M, Karthikeyan G, Vitola JV, Mahmarian JJ, et al. Current worldwide nuclear cardiology practices and radiation exposure: Results from the 65 country IAEA Nuclear Cardiology Protocols Cross-Sectional Study (INCAPS). *Eur Heart J* 2015; **36:** 1689–1696. PMID: 25898845
236. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. *Circulation* 2007; **116:** 1290–1305. PMID: 17846343
237. Chikamori T, Hida S, Tanaka N, Igarashi Y, Yamashita J, Shiba C, et al. Diagnostic performance of a cadmium-zinc-telluride single-photon emission computed tomography system with low-dose technetium-99m as assessed by fractional flow reserve. *Circ J* 2016; **80:** 1217–1224. PMID: 27053432
238. Duvall WL, Sweeny JM, Croft LB, Ginsberg E, Guma KA, Henzlova MJ. Reduced stress dose with rapid acquisition CZT SPECT MPI in a non-obese clinical population: Comparison to coronary angiography. *J Nucl Cardiol* 2012; **19:** 19–27. PMID: 22147617
239. Duvall WL, Croft LB, Ginsberg ES, Einstein AJ, Guma KA, George T, et al. Reduced isotope dose and imaging time with a high-efficiency CZT SPECT camera. *J Nucl Cardiol* 2011; **18:** 847–857. PMID: 21528422
240. Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate use criteria for cardiac radionuclide imaging: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *J Am Coll Cardiol* 2009; **53:** 2201–2229. PMID: 19497454
241. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. *J Nucl Cardiol* 2016; **23:** 606–639. PMID: 26914678

242. Hendel RC, Jamil T, Glover DK. Pharmacologic stress testing: New methods and new agents. *J Nucl Cardiol* 2003; **10:** 197–204. PMID: 12673185
243. Thomas GS, Miyamoto MI. Should simultaneous exercise become the standard for adenosine myocardial perfusion imaging? *Am J Cardiol* 2004; **94**(Suppl)**:** 3D–10D. PMID: 15261124
244. Kubo S, Tadamura E, Toyoda H, Mamede M, Yamamuro M, Magata Y, et al. Effect of caffeine intake on myocardial hyperemic flow induced by adenosine triphosphate and dipyridamole. *J Nucl Med* 2004; **45:** 730–738. PMID: 15136619
245. Elhendy A, Bax JJ, Poldermans D. Dobutamine stress myocardial perfusion imaging in coronary artery disease. *J Nucl Med* 2002; **43:** 1634–1646. PMID: 12468513
246. Travain MI, Wexler JP. Pharmacological stress testing. *Semin Nucl Med* 1999; **29:** 298–318. PMID: 10534233
247. He ZX, Hedrick TD, Pratt CM, Verani MS, Aquino V, Roberts R, et al. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation* 2000; **101:** 244–251. PMID: 10645919
248. Bavishi C, Argulian E, Chatterjee S, Rozanski A. CACS and the Frequency of stress-induced myocardial ischemia during MPI: A meta-analysis. *JACC Cardiovasc Imaging* 2016; **9:** 580–589. PMID: 27085440
249. Yuoness SA, Goha AM, Romsa JG, Akincioglu C, Warrington JC, Datta S, et al. Very high coronary artery calcium score with normal myocardial perfusion SPECT imaging is associated with a moderate incidence of severe coronary artery disease. *Eur J Nucl Med Mol Imaging* 2015; **42:** 1542–1550. PMID: 26138459
250. Berman DS, Wong ND, Gransar H, Miranda-Peats R, Dahlbeck J, Hayes SW, et al. Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *J Am Coll Cardiol* 2004; **44:** 923–930. PMID: 15312881
251. Einstein AJ, Johnson LL, Bokhari S, Son J, Thompson RC, Bateman TM, et al. Agreement of visual estimation of coronary artery calcium from low-dose CT attenuation correction scans in hybrid PET/CT and SPECT/CT with standard Agatston score. *J Am Coll Cardiol* 2010; **56:** 1914–1921. PMID: 21109114
252. Zellweger MJ, Haaf P, Maraun M, Osterhues HH, Keller U, Müller-Brand J, et al; BARDOT Investigators. Predictors and prognostic impact of silent coronary artery disease in asymptomatic high-risk patients with diabetes mellitus. *Int J Cardiol* 2017; **244:** 37–42. PMID: 28784453
253. Caobelli F, Haaf P, Chronis J, Haenny G, Brinkert M, Pfisterer ME, et al; Basel Asymptomatic High-Risk Diabetics' Outcome Trial (BARDOT) Investigators. Prognostic usefulness of cardiac stress test modalities in patients with type 2 diabetes mellitus who underwent myocardial perfusion scintigraphy (from the Basel Asymptomatic High-Risk Diabetics' Outcome Trial). *Am J Cardiol* 2017; **120:** 1098–1103. PMID: 28807404
254. Chang SM, Nabi F, Xu J, Pratt CM, Mahmarian AC, Frias ME, et al. Value of CACS compared with ETT and myocardial perfusion imaging for predicting long-term cardiac outcome in asymptomatic and symptomatic patients at low risk for coronary disease: Clinical implications in a multimodality imaging world. *JACC Cardiovasc Imaging* 2015; **8:** 134–144. PMID: 25677886
255. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, et al; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: The DIAD study. *Diabetes Care* 2004; **27:** 1954–1961. PMID: 15277423
256. Wackers FJ, Chyun DA, Young LH, Heller GV, Iskandrian AE, Davey JA, et al; Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators. Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Care* 2007; **30:** 2892–2898. PMID: 17682123
257. de Jong MC, Genders TS, van Geuns RJ, Moelker A, Hunink MG. Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: A systematic review and meta-analysis. *Eur Radiol* 2012; **22:** 1881–1895. PMID: 22527375
258. Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis. *J Am Coll Cardiol* 2012; **60:** 1828–1837. PMID: 23040573
259. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Equivalence between adenosine and exercise thallium-201 myocardial tomography: A multicenter, prospective, crossover trial. *J Am Coll Cardiol* 1992; **20:** 265–275. PMID: 1634661
260. Sakata Y, Nishimura T, Yamazaki J, Nishimura S, Kaivyas T, Kodama K, et al. Diagnosis of coronary artery disease by thallium-201 myocardial scintigraphy with intravenous infusion of SUNY4001 (adenosine) in effort angina pectoris: The clinical trial report at multi-center: Phase II. *Kaku Igaku* 2004; **41:** 123–132 (in Japanese). PMID: 15354725
261. Nishimura S, Nishimura T, Yamazaki J, Doi O, Konishi T, Iwasaki T, et al. Comparison of myocardial perfusion imaging by thallium-201 single-photon emission computed tomography with SUNY4001 (adenosine) and exercise: Crossover clinical trial at multi-center. *Kaku Igaku* 2004; **41:** 143–154 (in Japanese). PMID: 15354727
262. Neglia D, Rovai D, Caselli C, Pietila M, Teresinska A, Aguadé-Bruix S, et al. EVINCI Study Investigators. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. *Circ Cardiovasc Imaging* 2015; **8:** e002179. PMID: 25711274
263. Danad I, Raijmakers PG, Driessen RS, Leipsic J, Raju R, Naoum C, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol* 2017; **2:** 1100–1107. PMID: 28813561
264. Dai N, Zhang X, Zhang Y, Hou L, Li W, Fan B, et al. Enhanced diagnostic utility achieved by myocardial blood analysis: A meta-analysis of noninvasive cardiac imaging in the detection of functional coronary artery disease. *Int J Cardiol* 2016; **221:** 665–673. PMID: 27423088
265. Danad I, Szymonifka J, Twisk JWR, Norgaard BL, Zarins CK, Knaapen P, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: A meta-analysis. *Eur Heart J* 2017; **38:** 991–998. PMID: 27141095
266. Aarnoudse WH, Botman KJ, Pijls NH. False-negative myocardial scintigraphy in balanced three-vessel disease, revealed by coronary pressure measurement. *Int J Cardiovasc Intervent* 2003; **5:** 67–71. PMID: 12745861
267. Shrestha U, Sciammarella M, Alhassen F, Yeghiazarians Y, Ellin J, Verdin E, et al. Measurement of absolute myocardial blood flow in humans using dynamic cardiac SPECT and $^{99m}$Tc-tetrofosmin: Method and validation. *J Nucl Cardiol* 2017; **24:** 268–277. PMID: 26715603
268. Nkoulou R, Fuchs TA, Pazhenkottil AP, Kuest SM, Ghadri JR, Stehli J. Absolute myocardial blood flow and flow reserve assessed by gated SPECT with gadmium-zinc-telluride detectors using $^{99m}$Tc-tetrofosmin: Head-to-head comparison with $^{13}$N-ammonia PET. *J Nucl Med* 2016; **57:** 1887–1892. PMID: 27363834
269. Shiraishi S, Sakamoto F, Tsuda N, Yoshida M, Tomiguchi S, Utsunomiya D, et al. Prediction of left main or 3-vessel disease using myocardial perfusion reserve on dynamic thallium-201 single-photon emission computed tomography with a semiconductor gamma camera. *Circ J* 2015; **79:** 623–631. PMID: 25746547
270. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): A prospective trial. *Lancet* 2012; **379:** 453–460. PMID: 22196944
271. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettle K, et al. MR-IMPACT Investigators. MR-IMPACT II: Magnetic resonance imaging for myocardial perfusion assessment in coronary artery disease trial: Perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: A comparative multicentre, multivendor trial. *Eur Heart J* 2013; **34:** 775–781. PMID: 22390914
272. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettle K, et al; MR-IMPACT investigators. Superior diagnostic performance of perfusion-cardiovascular magnetic resonance versus SPECT to detect coronary artery disease: The secondary endpoints of the multicenter multivendor MR-IMPACT II (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial). *J Cardiovasc Magn Reson* 2012; **14:** 61. PMID: 22938651
273. Sharir T, Rabinowitz B, Livschitz S, Moalem I, Baron J, Kaplinsky E, et al. Underestimation of extent and severity of coronary artery disease by dipyridamole stress thallium-201

single-photon emission computed tomographic myocardial perfusion imaging in patients taking antianginal drugs. *J Am Coll Cardiol* 1998; **31:** 1540–1546. PMID: 9626832
274. Reyes E, Stirrup J, Roughton M, D'Souza S, Underwood SR, Anagnostopoulos C. Attenuation of adenosine-induced myocardial perfusion heterogeneity by atenolol and other cardioselective $\beta$-adrenoceptor blockers: A crossover myocardial perfusion imaging study. *J Nucl Med* 2010; **51:** 1036–1043. PMID: 20554740
275. Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. *J Am Coll Cardiol* 1993; **22:** 665–670. PMID: 8354796
276. Hachamovitch R, Berman DS, Shaw LJ, Kiat H, Cohen I, Cabico JA, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: Differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 1998; **97:** 535–543. PMID: 9494023
277. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol* 2004; **11:** 171–185. PMID: 15052249
278. Matsuo S, Nakajima K, Horie M, Nakae I, Nishimura T, J-ACCESS Investigators. Prognostic value of normal stress myocardial perfusion imaging in Japanese population: A study based on the J-ACCESS study. *Circ J* 2008; **72:** 611–617. PMID: 18362434
279. Chamuleau SA, Tio RA, de Cock CC, de Muinck ED, Pijls NH, van Eck-Smit BL, et al; Intermediate Lesions: Intracoronary flow Assessment versus $^{99m}$Tc-MIBI SPECT (ILIAS) Investigators. Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary narrowings and multivessel disease. *J Am Coll Cardiol* 2002; **39:** 852–858. PMID: 11869852
280. Chamuleau SA, Meuwissen M, Koch KT, van Eck-Smit BL, Tio RA, Tijssen JG, et al. Usefulness of fractional flow reserve for risk stratification of patients with multivessel coronary artery disease and an intermediate stenosis. *Am J Cardiol* 2002; **89:** 377–380. PMID: 11835914
281. Sharir T, Germano G, Kang X, Lewin HC, Miranda R, Cohen I, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: Risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. *J Nucl Med* 2001; **42:** 831–837. PMID: 11390544
282. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015; **372:** 1291–1300. PMID: 25773919
283. Karthikeyan G, Guzic Salobir B, Jug B, Devasenapathy N, Alexanderson E, Vitola J, et al. Functional compared to anatomical imaging in the initial evaluation of patients with suspected coronary artery disease: An international, multi-center, randomized controlled trial (IAEA-SPECT/CTA study). *J Nucl Cardiol* 2017; **24:** 507–517. PMID: 27796852
284. Yamauchi T, Tamaki N, Kasanuki H, Kimura T, Uemura Y, Iimuro S; Japanese Coronary-Angiography or Myocardial Imaging for Angina Pectoris Study (J-COMPASS) Multicenter Study Group. Optimal initial diagnostic strategies for the evaluation of stable angina patients: A multicenter, prospective study on myocardial perfusion imaging, computed tomographic angiography, and coronary angiography. *Circ J* 2012; **76:** 2832–2839. PMID: 22975716
285. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356:** 1503–1516. PMID: 17387127
286. Hori Y, Yoda S, Nakanishi K, Tano A, Suzuki Y, Matsumoto N, et al. Myocardial ischemic reduction evidenced by gated myocardial perfusion imaging after treatment results in good prognosis in patients with coronary artery disease. *J Cardiol* 2015; **65:** 278–284. PMID: 25082293
287. Nanasato M, Matsumoto N, Nakajima K, Chikamori T, Moroi M, Takehana K, et al. Prognostic impact of reducing myocardial ischemia identified using ECG-gated myocardial perfusion SPECT in Japanese patients with coronary artery disease: J-ACCESS 4 study. *Int J Cardiol* 2018; **267:** 202–207. PMID: 29859707
288. Yamasaki Y, Nakajima K, Kusuoka H, Izumi T, Kashiwagi A, Kawamori R, et al. Prognostic value of gated myocardial perfusion imaging for asymptomatic patients with type 2 diabetes: The J-ACCESS 2 investigation. *Diabetes Care* 2010; **33:** 2320–2326. PMID: 20724653
289. Nakamura S, Kawano Y, Nakajima K, Hase H, Joki N, Hatta T, et al. Prognostic study of cardiac events in Japanese patients with chronic kidney disease using ECG-gated myocardial Perfusion imaging: Final 3-year report of the J-ACCESS 3 study. *J Nucl Cardiol* 2019; **26:** 431–440. PMID: 28439760
290. Nakajima K, Matsuo S, Okuyama C, Hatta T, Tsukamoto K, Nishimura S, et al. Cardiac event risk in Japanese subjects estimated using gated myocardial perfusion imaging, in conjunction with diabetes mellitus and chronic kidney disease. *Circ J* 2012; **76:** 168–175. PMID: 22104035
291. Amer H, Niaz K, Hatazawa J, Gasmelseed A, Samiri HA, Al Othman M, et al. Future cardiac events in patients with ischemic ECG changes during adenosine infusion as a myocardial stress agent and normal cardiac scan. *Nucl Med Commun* 2017; **38:** 932–936. PMID: 28902766
292. Abbott BG, Afshar M, Berger AK, Wackers FJ. Prognostic significance of ischemic electrocardiographic changes during adenosine infusion in patients with normal myocardial perfusion imaging. *J Nucl Cardiol* 2003; **10:** 9–16. PMID: 12569326
293. Azemi T, Rai M, Parwani P, Baghdasarian S, Kazi F, Ahlberg AW et al. Electrocardiographic changes during vasodilator SPECT myocardial perfusion imaging: Does it affect diagnosis or prognosis? *J Nucl Cardiol* 2012; **19:** 84–91. PMID: 21947978
294. Chow BJ, Wong JW, Yoshinaga K, Ruddy TD, Williams K, deKemp RA, et al. Prognostic significance of dipyridamole-induced ST depression in patients with normal $^{82}$Rb PET myocardial perfusion imaging. *J Nucl Med* 2005; **46:** 1095–1101. PMID: 16000277
295. Ohtaki Y, Chikamori T, Hida S, Tanaka H, Igarashi Y, Hatano T, et al. Clinical characteristics in patients showing ischemic electrocardiographic changes during adenosine triphosphate loading single-photon emission computed tomography. *J Cardiol* 2010; **55:** 370–376. PMID: 20350503
296. Doukky R, Olusanya A, Vashistha R, Saini A, Fughhi I, Mansour K, et al. Diagnostic and prognostic significance of ischemic electrocardiographic changes with regadenoson-stress myocardial perfusion imaging. *J Nucl Cardiol* 2015; **22:** 700–713. PMID: 25907352
297. Takehana K, Nishimura S, Maeba H, Ueyama T, Iwasaka T, Nishimura T. Clinical significance of ischemic electrocardiographic changes during stress myocardial perfusion imaging: Sub-analysis of the J-ACCESS study. *Ann Nucl Med* 2010; **24:** 215–224. PMID: 20177833
298. Iqbal FM, Al Jaroudi W, Sanam K, Sweeney A, Heo J, Iskandrian AE, et al. Reclassification of cardiovascular risk in patients with normal myocardial perfusion imaging using heart rate response to vasodilator stress. *Am J Cardiol* 2013; **111:** 190–195. PMID: 23111139
299. AlJaroudi W, Campagnoli T, Fughhi I, Wassouf M, Ali A, Doukky R. Prognostic value of heart rate response during regadenoson stress myocardial perfusion imaging in patients with end stage renal disease. *J Nucl Cardiol* 2016; **23:** 560–569. PMID: 26293358
300. Moroi M, Yamashina A, Tsukamoto K, Nishimura T. J-ACCESS Investigators. Coronary revascularization does not decrease cardiac events in patients with stable ischemic heart disease but might do in those who showed moderate to severe ischemia. *Int J Cardiol* 2012; **158:** 246–252. PMID: 21342709
301. Schinkel AF, Bax JJ, Poldermans D, Elhendy A, Ferrari R, Rahimtoola SH. Hibernating myocardium: Diagnosis and patient outcomes. *Curr Probl Cardiol* 2007; **32:** 375–410. PMID: 17560992
302. Tamaki N, Kawamoto M, Tadamura E, Magata Y, Yonekura Y, Nohara R, et al. Prediction of reversible ischemia after revascularization: Perfusion and metabolic studies with positron emission tomography. *Circulation* 1995; **91:** 1697–1705. PMID: 7882476
303. Acampa W, Cuocolo A, Petretta M, Bruno A, Castellani M, Finzi A et al. Tetrofosmin imaging in the detection of myocardial viability in patients with previous myocardial infarction: Comparison with sestamibi and Tl-201 scintigraphy. *J Nucl Cardiol* 2002; **9:** 33–40. PMID: 11845127
304. Nakajima K, Tamaki N, Kuwabara Y, Kawano M, Matsunari I, Taki J et al. Prediction of functional recovery after revascularization using quantitative gated myocardial perfusion SPECT: A multi-center cohort study in Japan. *Eur J Nucl Med Mol Imaging* 2008; **35:** 2038–2048. PMID: 18504576

305. Matsunari I, Fujino S, Taki J, Senma J, Aoyama T, Wakasugi T, Hirai J, et al. Quantitative rest technetium-99m tetrofosmin imaging in predicting functional recovery after revascularization: Comparison with rest-redistribution thallium-201. *J Am Coll Cardiol* 1997; **29:** 1226–1233. PMID: 9137217
306. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: A meta-analysis. *J Am Coll Cardiol* 2002; **39:** 1151–1158. PMID: 11923039
307. Bonow RO, Maurer G, Lee KL, Holly TA, Binkley PF, Desvigne-Nickens P, et al; STICH Trial Investigators. Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med* 2011; **364:** 1617–1625. PMID: 21463153
308. Bonow RO, Castelvecchio S, Panza JA, Berman DS, Velazquez EJ, Michler RE, et al; STICH Trial Investigators. Severity of remodeling, myocardial viability, and survival in ischemic LV dysfunction after surgical revascularization. *JACC Cardiovasc Imaging* 2015; **8:** 1121–1129. PMID: 26363840
309. Beanlands RS, Nichol G, Huszti E, Humen D, Racine N, Freeman M, et al; PARR-2 Investigators. F-18-fluorodeoxyglucose positron emission tomography imaging-assisted management of patients with severe left ventricular dysfunction and suspected coronary disease: A randomized, controlled trial (PARR-2). *J Am Coll Cardiol* 2007; **50:** 2002–2012. PMID: 17996568
310. D'Egidio G, Nichol G, Williams KA, Guo A, Garrard L, deKemp R, et al; PARR-2 Investigators. Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: A substudy of the PARR-2 trial. *JACC Cardiovasc Imaging* 2009; **2:** 1060–1068. PMID: 19761983
311. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD, et al. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: Inducible ischemia versus hibernating myocardium. *Circ Cardiovasc Imaging* 2013; **6:** 363–372. PMID: 23595888
312. Senior R, Lahiri A, Kaul S. Effect of revascularization on left ventricular remodeling in patients with heart failure from severe chronic ischemic left ventricular dysfunction. *Am J Cardiol* 2001; **88:** 624–629. PMID: 11564384
313. Johnson NP, Kirkeeide RL, Gould KL. Is discordance of coronary flow reserve and fractional flow reserve due to methodology or clinically relevant coronary pathophysiology? *JACC Cardiovasc Imaging* 2012; **5:** 193–202. PMID: 22340827
314. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, et al; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009; **360:** 213–224. PMID: 19144937
315. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012; **367:** 991–1001. PMID: 22924638
316. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011; **124:** e574–e651. PMID: 22064601
317. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; **35:** 2541–2619. PMID: 25173339
318. van de Hoef TP, van Lavieren MA, Damman P, Delewi R, Piek MA, Chamuleau SA, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. *Circ Cardiovasc Interv* 2014; **7:** 301–311. PMID: 24782198
319. Samady H, Lepper W, Powers ER, Wei K, Ragosta M, Bishop GG, et al. Fractional flow reserve of infarct-related arteries identifies reversible defects on noninvasive myocardial perfusion imaging early after myocardial infarction. *J Am Coll Cardiol* 2006; **47:** 2187–2193. PMID: 16750683
320. Agarwal SK, Kasula S, Edupuganti MM, Raina S, Shailesh F, Almomani A, et al. Clinical decision-making for the hemodynamic "gray zone" (FFR 0.75–0.80) and long-term outcomes. *J Invasive Cardiol* 2017; **29:** 371–376. PMID: 28420802
321. Yamashita J, Tanaka N, Shindo N, Ogawa M, Kimura Y, Sakoda K, et al. Seven-year clinical outcomes of patients with moderate coronary artery stenosis after deferral of revascularization based on gray-zone fractional flow reserve. *Cardiovasc Interv Ther* 2015; **30:** 209–215. PMID: 25298079
322. Storto G, Cirillo P, Vicario ML, Pellegrino T, Sorrentino AR, Petretta M, et al. Estimation of coronary flow reserve by Tc-99m sestamibi imaging in patients with coronary artery disease: Comparison with the results of intracoronary Doppler technique. *J Nucl Cardiol* 2004; **11:** 682–688. PMID: 15592191
323. Kim YH, Ahn JM, Park DW, Song HG, Lee JY, Kim WJ, et al. Impact of ischemia-guided revascularization with myocardial perfusion imaging for patients with multivessel coronary disease. *J Am Coll Cardiol* 2012; **60:** 181–190. PMID: 22789882
324. Kusukawa J, Hirota Y, Kawamura K, Suma H, Takeuchi A, Adachi I, et al. Efficacy of coronary artery bypass surgery with gastroepiploic artery: Assessment with thallium 201 myocardial scintigraphy. *Circulation* 1989; **80:** I135–I140. PMID: 2788530
325. DePuey EG. Myocardial perfusion imaging with thallium-201 to evaluate patients before and after percutaneous transluminal coronary angioplasty. *Circulation* 1991; **84**(Suppl)**:** I59–I65. PMID: 1884506
326. Georgoulias P, Demakopoulos N, Kontos A, Xaplanteris P, Thomadakis K, Mortzos G, et al. Tc-99m tetrofosmin myocardial perfusion imaging before and six months after percutaneous transluminal coronary angioplasty. *Clin Nucl Med* 1998; **23:** 678–682. PMID: 9790042
327. Takeishi Y, Tono-oka I, Kubota I, Ikeda K, Masakane I, Chiba J, et al. Functional recovery of hibernating myocardium after coronary bypass surgery: Does it coincide with improvement in perfusion? *Am Heart J* 1991; **122:** 665–670. PMID: 1877443
328. Zellweger MJ, Weinbacher M, Zutter AW, Jeger RV, Mueller-Brand J, Kaiser C, et al. Long-term outcome of patients with silent versus symptomatic ischemia six months after percutaneous coronary intervention and stenting. *J Am Coll Cardiol* 2003; **42:** 33–40. PMID: 12849656
329. Zellweger MJ, Fahrni G, Ritter M, Jeger RV, Wild D, Buser P, et al; BASKET Investigators. Prognostic value of "routine" cardiac stress imaging 5 years after percutaneous coronary intervention: The prospective long-term observational BASKET (Basel Stent Kosteneffektivitäts Trial) LATE IMAGING study. *JACC Cardiovasc Interv* 2014; **7:** 615–621. PMID: 24835324
330. Germano G, Kavanagh PB, Slomka PJ, Van Kriekinge SD, Pollard G, Berman DS. Quantitation in gated perfusion SPECT imaging: The Cedars-Sinai approach. *J Nucl Cardiol* 2007; **14:** 433–454. PMID: 17679052
331. Garcia EV, Faber TL, Cooke CD, Folks RD, Chen J, Santana C. The increasing role of quantification in clinical nuclear cardiology: The Emory approach. *J Nucl Cardiol* 2007; **14:** 420–432. PMID: 17679051
332. Ficaro EP, Lee BC, Kritzman JN, Corbett JR. Corridor4DM: The Michigan method for quantitative nuclear cardiology. *J Nucl Cardiol* 2007; **14:** 455–465. PMID: 17679053
333. Germano G, Kiat H, Kavanagh PB, Moriel M, Mazzanti M, Su HT, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. *J Nucl Med* 1995; **36:** 2138–2147. PMID: 7472611
334. Faber TL, Cooke CD, Folks RD, Vansant JP, Nichols KJ, DePuey EG, et al. Left ventricular function and perfusion from gated SPECT perfusion images: An integrated method. *J Nucl Med* 1999; **40:** 650–659. PMID: 10210225
335. Nakajima K, Okuda K, Nyström K, Richter J, Minarik D, Wakabayashi H, et al. Improved quantification of small hearts for gated myocardial perfusion imaging. *Eur J Nucl Med Mol Imaging* 2013; **40:** 1163–1170. PMID: 23632963
336. Nakae I, Hayashi H, Matsumoto T, Mitsunami K, Horie M. Clinical usefulness of a novel program "Heart Function View" for evaluating cardiac function from gated myocardial perfusion SPECT. *Ann Nucl Med* 2014; **28:** 812–823. PMID: 25023232
337. Manrique A, Faraggi M, Véra P, Vilain D, Lebtahi R, Cribier A, et al. $^{201}$Tl and $^{99m}$Tc-MIBI gated SPECT in patients with large perfusion defects and left ventricular dysfunction: Comparison with equilibrium radionuclide angiography. *J Nucl Med* 1999; **40:** 805–809. PMID: 10319754

338. Cwajg E, Cwajg J, He ZX, Hwang WS, Keng F, Nagueh SF, et al. Gated myocardial perfusion tomography for the assessment of left ventricular function and volumes: Comparison with echocardiography. *J Nucl Med* 1999; **40:** 1857–1865. PMID: 10565781
339. Bavelaar-Croon CD, Kayser HW, van der Wall EE, de Roos A, Dibbets-Schneider P, Pauwels EK, et al. Left ventricular function: Correlation of quantitative gated SPECT and MR imaging over a wide range of values. *Radiology* 2000; **217:** 572–575. PMID: 11058662
340. Ioannidis JP, Trikalinos TA, Danias PG. Electrocardiogram-gated single-photon emission computed tomography versus cardiac magnetic resonance imaging for the assessment of left ventricular volumes and ejection fraction: A meta-analysis. *J Am Coll Cardiol* 2002; **39:** 2059–2068. PMID: 12084609
341. Nichols K, Lefkowitz D, Faber T, Folks R, Cooke D, Garcia EV, et al. Echocardiographic validation of gated SPECT ventricular function measurements. *J Nucl Med* 2000; **41:** 1308–1314. PMID: 10945519
342. Schepis T, Gaemperli O, Koepfli P, Valenta I, Strobel K, Brunner A, et al. Comparison of 64-slice CT with gated SPECT for evaluation of left ventricular function. *J Nucl Med* 2006; **47:** 1288–1294. PMID: 16883007
343. Tadamura E, Kudoh T, Motooka M, Inubushi M, Shirakawa S, Hattori N, et al. Assessment of regional and global left ventricular function by reinjection T1–201 and rest Tc-99m sestamibi ECG-gated SPECT: Comparison with three-dimensional magnetic resonance imaging. *J Am Coll Cardiol* 1999; **33:** 991–997. PMID: 10091826
344. Yoshioka J, Hasegawa S, Yamaguchi H, Tokita N, Paul AK, Xiuli M, et al. Left ventricular volumes and ejection fraction calculated from quantitative electrocardiographic-gated $^{99m}$Tc-tetrofosmin myocardial SPECT. *J Nucl Med* 1999; **40:** 1693–1698. PMID: 10520710
345. Nakajima K, Higuchi T, Taki J, Kawano M, Tonami N, et al. Accuracy of ventricular volume and ejection fraction measured by gated myocardial SPECT: Comparison of 4 software programs. *J Nucl Med* 2001; **42:** 1571–1578. PMID: 11585875
346. Schaefer WM, Lipke CS, Standke D, Kühl HP, Nowak B, Kaiser HJ, et al. Quantification of left ventricular volumes and ejection fraction from gated $^{99m}$Tc-MIBI SPECT: MRI validation and comparison of the Emory Cardiac Tool Box with QGS and 4D-MSPECT. *J Nucl Med* 2005; **46:** 1256–1263. PMID: 16085580
347. Nakajima K. Normal values for nuclear cardiology: Japanese databases for myocardial perfusion, fatty acid and sympathetic imaging and left ventricular function. *Ann Nucl Med* 2010; **24:** 125–135. PMID: 20108130
348. Nakajima K, Matsumoto N, Kasai T, Matsuo S, Kiso K, Okuda K. Normal values and standardization of parameters in nuclear cardiology: Japanese Society of Nuclear Medicine working group database. *Ann Nucl Med* 2016; **30:** 188–199. PMID: 26897008
349. Inubushi M, Tadamura E, Kudoh T, Hattori N, Kubo S, Koshiji T, et al. Simultaneous assessment of myocardial free fatty acid utilization and left ventricular function using $^{123}$I-BMIPP-gated SPECT. *J Nucl Med* 1999; **40:** 1840–1847. PMID: 10565779
350. Nanasato M, Ando A, Isobe S, Nonokawa M, Hirayama H, Tsuboi N, et al. Evaluation of left ventricular function using electrocardiographically gated myocardial SPECT with $^{123}$I-labeled fatty acid analog. *J Nucl Med* 2001; **42:** 1747–1756. PMID: 11752069
351. Kikkawa M, Nakamura T, Sakamoto K, Sugihara H, Azuma A, Sawada T, et al. Assessment of left ventricular diastolic function from quantitative electrocardiographic-gated $^{99m}$Tc-tetrofosmin myocardial SPET. *Eur J Nucl Med* 2001; **28:** 593–601. PMID: 11383864
352. Kumita S, Cho K, Nakajo H, Toba M, Uwamori M, Mizumura, et al. Assessment of left ventricular diastolic function with electrocardiography-gated myocardial perfusion SPECT: Comparison with multigated equilibrium radionuclide angiography. *J Nucl Cardiol* 2001; **8:** 568–574. PMID: 11593221
353. Nakajima K, Taki J, Kawano M, Higuchi T, Sato S, Nishijima, et al. Diastolic dysfunction in patients with systemic sclerosis detected by gated myocardial perfusion SPECT: An early sign of cardiac involvement. *J Nucl Med* 2001; **42:** 183–188. PMID: 11216514
354. Higuchi T, Nakajima K, Taki J, Kinuya S, Bunko H, Tonami N, et al. Assessment of left ventricular systolic and diastolic function based on the edge detection method with myocardial ECG-gated SPET. *Eur J Nucl Med* 2001; **28:** 1512–1516. PMID: 11685494
355. Sakamoto K, Nakamura T, Zen K, Hikosaka T, Nakamura T, Yamano T, et al. Identification of exercise-induced left ventricular systolic and diastolic dysfunction using gated SPECT in patients with coronary artery disease. *J Nucl Cardiol* 2004; **11:** 152–158. PMID: 15052246
356. Akhter N, Nakajima K, Okuda K, Matsuo S, Yoneyama T, Taki J, et al. Regional wall thickening in gated myocardial perfusion SPECT in a Japanese population: Effect of sex, radiotracer, rotation angles and frame rates. *Eur J Nucl Med Mol Imaging* 2008; **35:** 1608–1615. PMID: 18443788
357. Toba M, Kumita S, Cho K, Ibuki C, Kumazaki T, Takano T. Usefulness of gated myocardial perfusion SPECT imaging soon after exercise to identify postexercise stunning in patients with single-vessel coronary artery disease. *J Nucl Cardiol* 2004; **11:** 697–703. PMID: 15592193
358. Usui Y, Chikamori T, Nakajima K, Hida S, Yamashina A, Nishimura T, et al; J-ACCESS Investigators. Prognostic value of post-ischemic stunning as assessed by gated myocardial perfusion single-photon emission computed tomography: A subanalysis of the J-ACCESS study. *Circ J* 2010; **74:** 1591–1599. PMID: 20571246
359. Muramatsu T, Matsumoto K, Nishimura S. Efficacy of the phase images in Fourier analysis using gated cardiac POOL-SPECT for determining the indication for cardiac resynchronization therapy. *Circ J* 2005; **69:** 1521–1526. PMID: 16308502
360. Chen J, Garcia EV, Folks RD, Cooke CD, Faber TL, Tauxe EL. Onset of left ventricular mechanical contraction as determined by phase analysis of ECG-gated myocardial perfusion SPECT imaging: Development of a diagnostic tool for assessment of cardiac mechanical dyssynchrony. *J Nucl Cardiol* 2005; **12:** 687–695. PMID: 16344231
361. Nakajima K, Okuda K, Matsuo S, Kiso K, Kinuya S, Garcia EV, et al. Comparison of phase dyssynchrony analysis using gated myocardial perfusion imaging with four software programs: Based on the Japanese Society of Nuclear Medicine working group normal database. *J Nucl Cardiol* 2017; **24:** 611–621. PMID: 26860109
362. Okuda K, Nakajima K, Matsuo S, Kashiwaya S, Yoneyama H, Shibutani T, et al. Comparison of diagnostic performance of four software packages for phase dyssynchrony analysis in gated myocardial perfusion SPECT. *EJNMMI Res* 2017; **7:** 27. PMID: 28337725
363. Chen CC, Shen TY, Chang MC, Hung GU, Chen WC, Kao CH, et al. Stress-induced myocardial ischemia is associated with early post-stress left ventricular mechanical dyssynchrony as assessed by phase analysis of $^{201}$Tl gated SPECT myocardial perfusion imaging. *Eur J Nucl Med Mol Imaging* 2012; **39:** 1904–1909. PMID: 22875446
364. Huang WS, Huang CH, Lee CL, Chen CP, Hung GU, Chen J. Relation of early post-stress left ventricular dyssynchrony and the extent of angiographic coronary artery disease. *J Nucl Cardiol* 2014; **21:** 1048–1056. PMID: 25245950
365. Igarashi Y, Chikamori T, Hida S, Tanaka H, Shiba C, Usui Y, et al. Usefulness of phase analysis to differentiate ischemic and non-ischemic etiologies of left ventricular systolic dysfunction in patients with heart failure. *Circ J* 2014; **78:** 141–150. PMID: 24172076
366. Henneman MM, Chen J, Dibbets-Schneider P, Stokkel MP, Bleeker GB, Ypenburg C, et al. Can LV dyssynchrony as assessed with phase analysis on gated myocardial perfusion SPECT predict response to CRT? *J Nucl Med* 2007; **48:** 1104–1111. PMID: 17574987
367. Boogers MM, Van Kriekinge SD, Henneman MM, Ypenburg C, Van Bommel RJ, Boersma E, et al. Quantitative gated SPECT-derived phase analysis on gated myocardial perfusion SPECT detects left ventricular dyssynchrony and predicts response to cardiac resynchronization therapy. *J Nucl Med* 2009; **50:** 718–725. PMID: 19403876
368. Uebleis C, Hellweger S, Laubender RP, Becker A, Sohn HY, Lehner S, et al. Left ventricular dyssynchrony assessed by gated SPECT phase analysis is an independent predictor of death in patients with advanced coronary artery disease and reduced left ventricular function not undergoing cardiac resynchronization therapy. *Eur J Nucl Med Mol Imaging* 2012; **39:** 1561–1569. PMID: 22752450
369. Mori H, Isobe S, Suzuki S, Unno K, Morimoto R, Kano N, et al. Prognostic value of left ventricular dyssynchrony evaluated

by gated myocardial perfusion imaging in patients with chronic kidney disease and normal perfusion defect scores. *J Nucl Cardiol* 2019; **26:** 288–297. PMID: 28432673
370. Nuyts J, Dupont P, Van den Maegdenbergh V, Vleugels S, Suetens P, Mortelmans L. A study of the liver–heart artifact in emission tomography. *J Nucl Med* 1995; **36:** 133–139. PMID: 7799067
371. Kasai T, Depuey EG, Shah AA, Merla VC. Impact of gating errors with electrocardiography gated myocardial perfusion SPECT. *J Nucl Cardiol* 2003; **10:** 709–711. PMID: 14668787
372. de Geus-Oei LF, Mavinkurve-Groothuis AM, Bellersen L, Gotthardt M, Oyen WJ, et al. Scintigraphic techniques for early detection of cancer treatment-induced cardiotoxicity. *J Nucl Med* 2011; **52:** 560–571. PMID: 21421717
373. Massardo T, Jaimovich R, Lavados H, Gutiérrez D, Rodríguez JC, Saavedra JM, et al. Comparison of radionuclide ventriculography using SPECT and planar techniques in different cardiac conditions. *Eur J Nucl Med Mol Imaging* 2007; **34:** 1735–1746. PMID: 17579852
374. Odagiri K, Wakabayashi Y, Tawarahara K, Kurata C, Urushida T, Katoh H, et al. Evaluation of right and left ventricular function by quantitative blood-pool SPECT (QBS): Comparison with conventional methods and quantitative gated SPECT (QGS). *Ann Nucl Med* 2006; **20:** 519–526. PMID: 17134018
375. Ellison JP, Williams TH. Sympathetic nerve pathways to the human heart, and their variations. *Am J Anat* 1969; **124:** 149–162. PMID: 5774648
376. Mitrani RD, Klein LS, Miles WM, Hackett FK, Burt RW, Wellman HN, et al. Regional cardiac sympathetic denervation in patients with ventricular tachycardia in the absence of coronary artery disease. *J Am Coll Cardiol* 1993; **22:** 1344–1353. PMID: 8227790
377. Wieland DM, Brown LE, Rogers WL, Worthington KC, Wu JL, Clinthorne NH, et al. Myocardial imaging with a radioiodinated norepinephrine storage analog. *J Nucl Med* 1981; **22:** 22–31. PMID: 7452352
378. Tobes MC, Jaques S Jr, Wieland DM, Sisson JC. Effect of uptake-one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med* 1985; **26:** 897–907. PMID: 3162008
379. Sisson JC, Wieland DM, Sherman P, Mangner TJ, Tobes MC, Jacques S Jr, et al. Metaiodobenzylguanidine as an index of the adrenergic nervous system integrity and function. *J Nucl Med* 1987; **28:** 1620–1624. PMID: 3655914
380. Flotats A, Carrió I, Agostini D, Le Guludec D, Marcassa C, Schäfers M. Proposal for standardization of $^{123}$I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. *Eur J Nucl Med Mol Imaging* 2010; **37:** 1802–1812. PMID: 20577740
381. Nakajima K, Okuda K, Matsuo S, Yoshita M, Taki J, Yamada M, et al. Standardization of metaiodobenzylguanidine heart to mediastinum ratio using a calibration phantom: Effects of correction on normal databases and a multicentre study. *Eur J Nucl Med Mol Imaging* 2012; **39:** 113–119. PMID: 22009380
382. Nakajima K, Okuda K, Yoshimura M, Matsuo S, Wakabayashi H, Imanishi Y, et al. Multicenter cross-calibration of I-123 metaiodobenzylguanidine heart-to-mediastinum ratios to overcome camera-collimator variations. *J Nucl Cardiol* 2014; **21:** 970–978. PMID: 24942608
383. Merlet P, Valette H, Dubois-Randé JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzylguanidine imaging in patients with heart failure. *J Nucl Med* 1992; **33:** 471–477. PMID: 1552326
384. Matsunari I, Schricke U, Bengel FM, Haase HU, Barthel P, Schmidt G, et al. Extent of cardiac sympathetic neuronal damage is determined by the area of ischemia in patients with acute coronary syndromes. *Circulation* 2000; **101:** 2579–2585. PMID: 10840008
385. Stanton MS, Tuli MM, Radtke NL, Heger JJ, Miles WM, Mock BH, et al. Regional sympathetic denervation after myocardial infarction in humans detected noninvasively using I-123-metaiodobenzylguanidine. *J Am Coll Cardiol* 1989; **14:** 1519–1526. PMID: 2809013
386. McGhie AI, Corbett JR, Akers MS, Kulkarni P, Sills MN, Kremers M, et al. Regional cardiac adrenergic function using I-123 meta-iodobenzylguanidine tomographic imaging after acute myocardial infarction. *Am J Cardiol* 1991; **67:** 236–242. PMID: 1990785
387. Simula S, Lakka T, Laitinen T, Remes J, Kettunen R, Kuikka J, et al. Cardiac adrenergic denervation in patients with non-Q-wave versus Q-wave myocardial infarction. *Eur J Nucl Med* 2000; **27:** 816–821. PMID: 10952493
388. Simões MV, Barthel P, Matsunari I, Nekolla SG, Schömig A, Schwaiger M, et al. Presence of sympathetically denervated but viable myocardium and its electrophysiologic correlates after early revascularised, acute myocardial infarction. *Eur Heart J* 2004; **25:** 551–557. PMID: 15120051
389. Nakata T, Nakajima K, Yamashina S, Yamada T, Momose M, Kasama S, et al. A pooled analysis of multicenter cohort studies of $^{123}$I-MIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. *JACC Cardiovasc Imaging* 2013; **6:** 772–784. PMID: 23845574
390. Nakajima K, Nakata T, Yamada T, Yamashina S, Momose M, Kasama S, et al. A prediction model for 5-year cardiac mortality in patients with chronic heart failure using $^{123}$I-metaiodobenzylguanidine imaging. *Eur J Nucl Med Mol Imaging* 2014; **41:** 1673–1682. PMID: 24663289
391. Jacobson AF, Senior R, Cerqueira MD, Wong ND, Thomas GS, Lopez VA, et al; ADMIRE-HF Investigators. Myocardial iodine-123 meta-iodobenzylguanidine imaging and cardiac events in heart failure: Results of the prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) study. *J Am Coll Cardiol* 2010; **55:** 2212–2221. PMID: 20188504
392. Narula J, Gerson M, Thomas GS, Cerqueira MD, Jacobson AF. $^{123}$I-MIBG imaging for prediction of mortality and potentially fatal events in heart failure: The ADMIRE-HFX study. *J Nucl Med* 2015; **56:** 1011–1018. PMID: 26069309
393. Boogers MJ, Borleffs CJ, Henneman MM, van Bommel RJ, van Ramshorst J, Boersma E, et al. Cardiac sympathetic denervation assessed with 123-iodine metaiodobenzylguanidine imaging predicts ventricular arrhythmias in implantable cardioverter-defibrillator patients. *J Am Coll Cardiol* 2010; **55:** 2769–2777. PMID: 20538172
394. Toyama T, Suzuki Y, Tsukagoshi J, Kanda T, Imai S, Murata K, et al. Usefulness of 123I-MIBG and 123I-BMIPP myocardial scintigraphy for detecting coronary artery disease and for evaluating left ventricular function. *Kaku Igaku* 1995; **32:** 173–181 (in Japanese). PMID: 7715103
395. Tsuchimochi S, Tamaki N, Tadamura E, Kawamoto M, Fujita T, Yonekura Y, et al. Age and gender differences in normal myocardial adrenergic neuronal function evaluated by iodine-123-MIBG imaging. *J Nucl Med* 1995; **36:** 969–974. PMID: 7769454
396. Yoshinaga K, Tomiyama Y, Manabe O, Kasai K, Katoh C, Magota K, et al. Prone-position acquisition of myocardial $^{123}$I-metaiodobenzylguanidine (MIBG) SPECT reveals regional uptake similar to that found using $^{11}$C-hydroxyephedrine PET/CT. *Ann Nucl Med* 2014; **28:** 761–769. PMID: 24950751
397. Clements IP, Kelkar AA, Garcia EV, Butler J, Chen J, Folks R, et al. Prognostic significance of $^{123}$I-mIBG SPECT myocardial imaging in heart failure: Differences between patients with ischaemic and non-ischaemic heart failure. *Eur Heart J Cardiovasc Imaging* 2016; **17:** 384–390. PMID: 26588983
398. Takeishi Y, Atsumi H, Fujiwara S, Takahashi K, Tomoike H. ACE inhibition reduces cardiac iodine-123-MIBG release in heart failure. *J Nucl Med* 1997; **38:** 1085–1089. PMID: 9225795
399. Yamazaki J, Muto H, Kabano T, Yamashina S, Nanjo S, Inoue A. Evaluation of $\beta$-blocker therapy in patients with dilated cardiomyopathy: Clinical meaning of iodine 123-metaiodobenzylguanidine myocardial single-photon emission computed tomography. *Am Heart J* 2001; **141:** 645–652. PMID: 11275933
400. Kasama S, Toyama T, Kumakura H, Takayama Y, Ichikawa S, Suzuki T, et al. Spironolactone improves cardiac sympathetic nerve activity and symptoms in patients with congestive heart failure. *J Nucl Med* 2002; **43:** 1279–1285. PMID: 12368364
401. Cohen-Solal A, Rouzet F, Berdeaux A, Le Guludec D, Abergel E, Syrota A, et al. Effects of carvedilol on myocardial sympathetic innervation in patients with chronic heart failure. *J Nucl Med* 2005; **46:** 1796–1803. PMID: 16269592
402. Kasama S, Toyama T, Hatori T, Sumino H, Kumakura H, Takayama Y, et al. Evaluation of cardiac sympathetic nerve activity and left ventricular remodelling in patients with dilated cardiomyopathy on the treatment containing carvedilol. *Eur Heart J* 2007; **28:** 989–995. PMID: 17409109
403. Erol-Yilmaz A, Verberne HJ, Schrama TA, Hrudova J, De Winter RJ, Van Eck-Smit BL, et al. Cardiac resynchronization induces favorable neurohumoral changes. *Pacing Clin Electro-*

*physiol* 2005; **28:** 304–310. PMID: 15826264
404. Burri H, Sunthorn H, Somsen A, Fleury E, Stettler C, Shah D, et al. Improvement in cardiac sympathetic nerve activity in responders to resynchronization therapy. *Europace* 2008; **10:** 374–378. PMID: 18308757
405. Tamaki N, Morita K, Kuge Y, Tsukamoto E. The role of fatty acids in cardiac imaging. *J Nucl Med* 2000; **41:** 1525–1534. PMID: 10994734
406. Yoshinaga K, Tamaki N. Imaging myocardial metabolism. *Curr Opin Biotechnol* 2007; **18:** 52–59. PMID: 17157495
407. Liedtke AJ. Alterations of carbohydrate and lipid metabolism in the acutely ischemic heart. *Prog Cardiovasc Dis* 1981; **23:** 321–336. PMID: 7012926
408. Neely JR, Rovetto MJ, Oram JF. Myocardial utilization of carbohydrate and lipids. *Prog Cardiovasc Dis* 1972; **15:** 289–329. PMID: 4564017
409. Knapp FF, Ambrose KR, Goodman MM. New radioiodinated methyl-branched fatty acids for cardiac studies. *Eur J Nucl Med* 1986; **12**(Suppl)**:** S39–S44. PMID: 3490376
410. Fujibayashi Y, Yonekura Y, Takemura Y, Wada K, Matsumoto K, Tamaki N, et al. Myocardial accumulation of iodinated beta-methyl-branched fatty acid analogue, iodine-125-15-(p-iodophenyl)-3-(R,S)methylpentadecanoic acid (BMIPP), in relation to ATP concentration. *J Nucl Med* 1990; **31:** 1818–1822. PMID: 2230994
411. Yoshinaga K, Matsuki T, Hashimoto A, Tsukamoto K, Nakata T, Tamaki N. Validation of automated quantitation of myocardial perfusion and fatty acid metabolism abnormalities on SPECT images. *Circ J* 2011; **75:** 2187–2195. PMID: 21747199
412. Nakata T, Hashimoto A, Matsuki T, Yoshinaga K, Tsukamoto K, Tamaki N. Prognostic value of automated SPECT scoring system for coronary artery disease in stress myocardial perfusion and fatty acid metabolism imaging. *Int J Cardiovasc Imaging* 2013; **29:** 253–262. PMID: 22782310
413. Taki J, Matsunari I. Metabolic imaging using SPECT. *Eur J Nucl Med Mol Imaging* 2007; **34**(Suppl)**:** S34–S48. PMID: 17479263
414. Schwaiger M, Schelbert HR, Ellison D, Hansen H, Yeatman L, Vinten-Johansen J, et al. Sustained regional abnormalities in cardiac metabolism after transient ischemia in the chronic dog model. *J Am Coll Cardiol* 1985; **6:** 336–347. PMID: 3874892
415. Hashimoto A, Nakata T, Tsuchihashi K, Tanaka S, Fujimori K, Iimura O, et al. Postischemic functional recovery and BMIPP uptake after primary percutaneous transluminal coronary angioplasty in acute myocardial infarction. *Am J Cardiol* 1996; **77:** 25–30. PMID: 8540452
416. Nakata T, Hashimoto A, Eguchi M. Cardiac BMIPP imaging in acute myocardial infarction. *Int J Card Imaging* 1999; **15:** 21–26. PMID: 10453399
417. Hatano T, Chikamori T, Usui Y, Morishima T, Hida S, Yamashina A. Diagnostic significance of positive I-123 BMIPP despite negative stress Tl-201 myocardial imaging in patients with suspected coronary artery disease. *Circ J* 2006; **70:** 184–189. PMID: 16434813
418. Takeishi Y, Atsumi H, Fujiwara S, Takahashi K, Tomoike H. Fatty acid metabolic imaging with 123I-BMIPP for the diagnosis of coronary artery disease: Application to patients with diabetes mellitus and hyperlipidaemia. *Nucl Med Commun* 1996; **17:** 675–680. PMID: 8878126
419. Yamabe H, Abe H, Yokoyama M, Shiotani H, Kajiya S, Mori T, et al. Resting $^{123}$I-BMIPP scintigraphy in diagnosis of effort angina pectoris with reference to subsets of the disease. *Ann Nucl Med* 1998; **12:** 139–144. PMID: 9673714
420. Fukuzawa S, Ozawa S, Shimada K, Sugioka J, Inagaki M, et al. Prognostic values of perfusion-metabolic mismatch in Tl-201 and BMIPP scintigraphic imaging in patients with chronic coronary artery disease and left ventricular dysfunction undergoing revascularization. *Ann Nucl Med* 2002; **16:** 109–115. PMID: 12043904
421. Dilsizian V, Bateman TM, Bergmann SR, Des Prez R, Magram MY, Goodbody AE, et al. Metabolic imaging with $\beta$-methyl-*p*-[$^{123}$I]-iodophenyl-pentadecanoic acid identifies ischemic memory after demand ischemia. *Circulation* 2005; **112:** 2169–2174. PMID: 16186423
422. Taki J, Nakajima K, Matsunari I, Bunko H, Takada S, Tonami N, et al. Impairment of regional fatty acid uptake in relation to wall motion and thallium-201 uptake in ischaemic but viable myocardium: Assessment with iodine-123-labelled beta-methyl-branched fatty acid. *Eur J Nucl Med* 1995; **22:** 1385–1392. PMID: 8586083
423. Saitoh M, Hasegawa K, Hasegawa K, Kondoh T, Yanagawa T. Detection of coronary artery disease using 12-lead electrocardiogram and simultaneous dual myocardial imaging with iodine-123-$\beta$-methyl iodophenyl-pentadecanoic acid (BMIPP) and thallium-201 in patients with unstable angina. *Intern Med* 1995; **34:** 1064–1070. PMID: 8774965
424. Takeishi Y, Sukekawa H, Saito H, Nishimura S, Shibu T, Sasaki Y, et al. Clinical significance of decreased myocardial uptake of 123I-BMIPP in patients with stable effort angina pectoris. *Nucl Med Commun* 1995; **16:** 1002–1008. PMID: 8719980
425. Ueshima K, Miyakawa T, Taniguchi Y, Nishiyama O, Musha T, Saitoh M, et al. The incidence of discrepant regional myocardial uptake between 201 thallium and 123 I-BMIPP SPECT in patients with coronary heart disease. *Int J Cardiovasc Imaging* 2002; **18:** 273–278. PMID: 12123320
426. Nakajima K, Shimizu K, Taki J, Uetani Y, Konishi S, Tonami N, et al. Utility of iodine-123-BMIPP in the diagnosis and follow-up of vasospastic angina. *J Nucl Med* 1995; **36:** 1934–1940. PMID: 7472578
427. Watanabe K, Ohta Y, Toba K, Ogawa Y, Aizawa Y, Tanabe N, et al. Abnormal fatty acid metabolism in patients with coronary vasospasm. *Ann Nucl Med* 1999; **13:** 33–41. PMID: 10202946
428. Kawai Y, Tsukamoto E, Nozaki Y, Morita K, Sakurai M, Tamaki N. Significance of reduced uptake of iodinated fatty acid analogue for the evaluation of patients with acute chest pain. *J Am Coll Cardiol* 2001; **38:** 1888–1894. PMID: 11738290
429. Yoneyama K, Akashi YJ, Kida K, Ashikaga K, Musha H, Suzuki K, et al. Metabolic planar imaging using $^{123}$I-$\beta$-methyl-iodophenyl pentadecanoic acid identifies myocardial ischemic memory after intracoronary acetylcholine provocation tests in patients with vasospastic angina. *Int Heart J* 2014; **55:** 113–118. PMID: 24632951
430. Sato H, Iwasaki T, Toyama T, Kaneko Y, Inoue T, Endo K, et al. Prediction of functional recovery after revascularization in coronary artery disease using $^{18}$F-FDG and $^{123}$I-BMIPP SPECT. *Chest* 2000; **117:** 65–72. PMID: 10631201
431. Shimonagata T, Nanto S, Kusuoka H, Ohara T, Inoue K, Yamada S, et al. Metabolic changes in hibernating myocardium after percutaneous transluminal coronary angioplasty and the relation between recovery in left ventricular function and free fatty acid metabolism. *Am J Cardiol* 1998; **82:** 559–563. PMID: 9732879
432. Taki J, Nakajima K, Matsunari I, Bunko H, Takata S, Kawasuji M et al. Assessment of improvement of myocardial fatty acid uptake and function after revascularization using iodine-123-BMIPP. *J Nucl Med* 1997; **38:** 1503–1510. PMID: 9379183
433. Fujita K, Kasama S, Kurabayashi M. Serial dual single-photon emission computed tomography of thallium-201 and iodine-123 beta-methyliodophenyl pentadecanoic acid scintigraphy can predict functional recovery of patients with coronary artery disease after coronary artery bypass graft surgery. *Nucl Med Commun* 2015; **36:** 148–155. PMID: 25321160
434. Hashimoto A, Nakata T, Tamaki N, Kobayashi T, Matsuki T, Shogase T, et al. Serial alterations and prognostic implications of myocardial perfusion and fatty acid metabolism in patients with acute myocardial infarction. *Circ J* 2006; **70:** 1466–1474. PMID: 17062973
435. Chikamori T, Fujita H, Nanasato M, Toba M, Nishimura T. Prognostic value of I-123 15-(p-iodophenyl)-3-(R,S) methylpentadecanoic acid myocardial imaging in patients with known or suspected coronary artery disease. *J Nucl Cardiol* 2005; **12:** 172–178. PMID: 15812371
436. Nanasato M, Hirayama H, Ando A, Isobe S, Nonokawa M, Kinoshita Y, et al. Incremental predictive value of myocardial scintigraphy with $^{123}$I-BMIPP in patients with acute myocardial infarction treated with primary percutaneous coronary intervention. *Eur J Nucl Med Mol Imaging* 2004; **31:** 1512–1521. PMID: 15232655
437. Nakata T, Kobayashi T, Tamaki N, Kobayashi H, Wakabayashi T, Shimoshige S, et al. Prognostic value of impaired myocardial fatty acid uptake in patients with acute myocardial infarction. *Nucl Med Commun* 2000; **21:** 897–906. PMID: 11130330
438. Inaba Y, Bergmann SR. Prognostic value of myocardial metabolic imaging with BMIPP in the spectrum of coronary artery disease: A systematic review. *J Nucl Cardiol* 2010; **17:** 61–70. PMID: 19851821

439. Matsuki T, Tamaki N, Nakata T, Doi A, Takahashi H, Iwata M, et al. Prognostic value of fatty acid imaging in patients with angina pectoris without prior myocardial infarction: Comparison with stress thallium imaging. *Eur J Nucl Med Mol Imaging* 2004; **31:** 1585–1591. PMID: 15583913
440. Abe H, Iguchi N, Utanohara Y, Inoue K, Takamisawa I, Seki A, et al. Non-invasive diagnosis of coronary artery disease by $^{123}$I-BMIPP/$^{201}$TlCl dual myocardial SPECT in patients with heart failure. *Int J Cardiol* 2014; **176:** 969–974. PMID: 25205480
441. Sasaki R, Mitani I, Usui T, Kitamura Y, Yoshii Y, Ishikawa T, et al. Clinical value of iodine-123 beta-methyliodophenyl pentadecanoic acid (BMIPP) myocardial single photon emission computed tomography for predicting cardiac death among patients with chronic heart failure. *Circ J* 2003; **67:** 918–924. PMID: 14578597
442. Yazaki Y, Isobe M, Takahashi W, Kitabayashi H, Nishiyama O, Sekiguchi M, et al. Assessment of myocardial fatty acid metabolic abnormalities in patients with idiopathic dilated cardiomyopathy using $^{123}$I BMIPP SPECT: Correlation with clinicopathological findings and clinical course. *Heart* 1999; **81:** 153–159. PMID: 9922350
443. Nishimura M, Hashimoto T, Kobayashi H, Fukuda T, Okino K, Yamamoto N, et al. Myocardial scintigraphy using a fatty acid analogue detects coronary artery disease in hemodialysis patients. *Kidney Int* 2004; **66:** 811–819. PMID: 15253738
444. Nishimura M, Murase M, Hashimoto T, Kobayashi H, Yamazaki S, Imai R, et al. Influence of diabetes mellitus on diagnostic potential of iodine-123-BMIPP imaging for coronary artery stenosis in hemodialysis patients. *J Nephrol* 2006; **19:** 481–491. PMID: 17048206
445. Nishimura M, Tsukamoto K, Hasebe N, Tamaki N, Kikuchi K, Ono T, et al. Prediction of cardiac death in hemodialysis patients by myocardial fatty acid imaging. *J Am Coll Cardiol* 2008; **51:** 139–145. PMID: 18191738
446. Nishimura M, Tokoro T, Nishida M, Hashimoto T, Kobayashi H, Yamazaki S, et al. Myocardial fatty acid imaging identifies a group of hemodialysis patients at high risk for cardiac death after coronary revascularization. *Kidney Int* 2008; **74:** 513–520. PMID: 18528325
447. Moroi M, Tamaki N, Nishimura M, Haze K, Nishimura T, Kusano E, et al. Association between abnormal myocardial fatty acid metabolism and cardiac-derived death among patients undergoing hemodialysis: Results from a cohort study in Japan. *Am J Kidney Dis* 2013; **61:** 466–475. PMID: 23201161
448. Momose M, Miyake Y, Fukushima K, Nakajima T, Kondo C, Hagiwara N, et al. Prognostic value of $^{123}$I-betamethyl-p-iodophenyl-pentadecanoic acid single-photon emission computed tomography in diabetic patients with suspected ischemic heart disease. *Circ J* 2012; **76:** 2633–2639. PMID: 22864180
449. Zen K, Tamaki N, Nishimura M, Nakatani E, Moroi M, Nishimura T, et al. Cardiac event risk stratification in patients with end-stage renal disease: Sub-analysis of the B-SAFE study. *Int J Cardiol* 2016; **202:** 694–700. PMID: 26454538
450. Nishimura M, Okamoto Y, Tokoro T, Sato N, Nishida M, Hashimoto T, et al. Clinical potential of oral nicorandil to improve myocardial fatty acid metabolism after percutaneous coronary intervention in hemodialysis patients. *Nephron Clin Pract* 2014; **126:** 24–32. PMID: 24434794
451. Nakata T, Hashimoto A, Moroi M, Tamaki N, Nishimura T, Hasebe N, et al. Sudden death prediction by C-reactive protein, electrocardiographic findings, and myocardial fatty acid uptake in haemodialysis patients: Analysis of a multicentre prospective cohort sub-study. *Eur Heart J Cardiovasc Imaging* 2016; **17:** 1394–1404. PMID: 26710818
452. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. *Circulation* 2008; **117:** 103–114. PMID: 18172050
453. Gallagher BM, Ansari A, Atkins H, Casella V, Christman DR, Fowler JS, et al. Radiopharmaceuticals XXVII. $^{18}$F-labeled 2-deoxy-2-fluoro-d-glucose as a radiopharmaceutical for measuring regional myocardial glucose metabolism in vivo: Tissue distribution and imaging studies in animals. *J Nucl Med* 1977; **18:** 990–996. PMID: 903484
454. Ratib O, Phelps ME, Huang SC, Henze E, Selin CE, Schelbert HR. Positron tomography with deoxyglucose for estimating local myocardial glucose metabolism. *J Nucl Med* 1982; **23:** 577–586. PMID: 6979614
455. Maes A, Flameng W, Nuyts J, Borgers M, Shivalkar B, Ausma J, et al. Histological alterations in chronically hypoperfused myocardium: Correlation with PET findings. *Circulation* 1994; **90:** 735–745. PMID: 8044942
456. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol* 2003; **42:** 1318–1333. PMID: 14522503
457. Abel ED. Glucose transport in the heart. *Front Biosci* 2004; **9:** 201–215. PMID: 14766360
458. Knuuti MJ, Nuutila P, Ruotsalainen U, Saraste M, Härkönen R, Ahonen A, et al. Euglycemic hyperinsulinemic clamp and oral glucose load in stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 1992; **33:** 1255–1262. PMID: 1613561
459. Machac J, Bacharach SL, Bateman TM, Bax JJ, Beanlands R, Bengel, et al; Quality Assurance Committee of the American Society of Nuclear Cardiology. Positron emission tomography myocardial perfusion and glucose metabolism imaging. *J Nucl Cardiol* 2006; **13:** e121–e151. PMID: 17174789
460. Hosono M, Senda M, Sasaki M, Momose T, Ito K, Okamura M, et al. FDG PET, PET/CT practice guidelines 2018 by Japanese Society of Nuclear Medicine. *Kaku-Igaku* 2018; **55:** A1–A22 (in Japanese). https://doi.org/10.18893/kakuigaku.gl.1881 (accessed Dec 25, 2019).
461. Brogsitter C, Grüning T, Weise R, Wielepp P, Lindner O, Körfer R, et al. $^{18}$F-FDG PET for detecting myocardial viability: Validation of 3D data acquisition. *J Nucl Med* 2005; **46:** 19–24. PMID: 15632028
462. Cornel JH, Bax JJ, Elhendy A, Visser FC, Boersma E, Poldermans Det al. Agreement and disagreement between "metabolic viability"and "contractile reserve" in akinetic myocardium. *J Nucl Cardiol* 1999; **6:** 383–388. PMID: 10461604
463. Mody FV, Brunken RC, Stevenson LW, Nienaber CA, Phelps ME, Schelbert HR, et al. Differentiating cardiomyopathy of coronary artery disease from nonischemic dilated cardiomyopathy utilizing positron emission tomography. *J Am Coll Cardiol* 1991; **17:** 373–383. PMID: 1991893
464. Maddahi J, Packard RR. Cardiac PET perfusion tracers: Current status and future directions. *Semin Nucl Med* 2014; **44:** 333–343. PMID: 25234078
465. Schelbert HR, Phelps ME, Huang SC, MacDonald NS, Hansen H, Selin C, et al. N-13 ammonia as an indicator of myocardial blood flow. *Circulation* 1981; **63:** 1259–1272. PMID: 7226473
466. Slomka PJ, Alexanderson E, Jácome R, Jiménez M, Romero E, Meave A, et al. Comparison of clinical tools for measurements of regional stress and rest myocardial blood flow assessed with $^{13}$N-ammonia PET/CT. *J Nucl Med* 2012; **53:** 171–181. PMID: 22228795
467. Machac J. Cardiac positron emission tomography imaging. *Semin Nucl Med* 2005; **35:** 17–36. PMID: 15645392
468. Parker MW, Iskandar A, Limone B, Perugini A, Kim H, Jones C, et al. Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: A bivariate meta-analysis. *Circ Cardiovasc Imaging* 2012; **5:** 700–707. PMID: 23051888
469. Chen A, Wang H, Fan B, Xu Y, Chen W, Dai N. Prognostic value of normal positron emission tomography myocardial perfusion imaging in patients with known or suspected coronary artery disease: A meta-analysis. *Br J Radiol* 2017; **90:** 20160702. PMID: 28306335
470. Marwick TH, Shan K, Patel S, Go RT, Lauer MS. Incremental value of rubidium-82 positron emission tomography for prognostic assessment of known or suspected coronary artery disease. *Am J Cardiol* 1997; **80:** 865–870. PMID: 9381999
471. Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L, et al. What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J Am Coll Cardiol* 2006; **48:** 1029–1039. PMID: 16949498
472. Dorbala S, Di Carli MF, Beanlands RS, Merhige ME, Williams BA, Veledar E, et al. Prognostic value of stress myocardial perfusion positron emission tomography: Results from a multicenter observational registry. *J Am Coll Cardiol* 2013; **61:** 176–184. PMID: 23219297
473. Pen A, Yam Y, Chen L, Dorbala S, Di Carli MF, Merhige ME, et al. Prognostic value of Rb-82 positron emission tomography myocardial perfusion imaging in coronary artery bypass

patients. *Eur Heart J Cardiovasc Imaging* 2014; **15:** 787–792. PMID: 24477784
474. Curtis JP, Sokol SI, Wang Y, Rathore SS, Ko DT, Jadbabaie F, et al. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. *J Am Coll Cardiol* 2003; **42:** 736–742. PMID: 12932612
475. Lertsburapa K, Ahlberg AW, Bateman TM, Katten D, Volker L, Cullom SJ, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. *J Nucl Cardiol* 2008; **15:** 745–753. PMID: 18984449
476. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation* 2011; **124:** 2215–2224. PMID: 22007073
477. Fiechter M, Ghadri JR, Gebhard C, Fuchs TA, Pazhenkottil AP, Nkoulou RN, et al. Diagnostic value of $^{13}$N-ammonia myocardial perfusion PET: Added value of myocardial flow reserve. *J Nucl Med* 2012; **53:** 1230–1234. PMID: 22776752
478. Ziadi MC, Dekemp RA, Williams K, Guo A, Renaud JM, Chow BJ, et al. Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? *J Nucl Cardiol* 2012; **19:** 670–680. PMID: 22415819
479. Naya M, Murthy VL, Taqueti VR, Foster CR, Klein J, Garber M, et al. Preserved coronary flow reserve effectively excludes high-risk coronary artery disease on angiography. *J Nucl Med* 2014; **55:** 248–255. PMID: 24408896
480. Huisman MC, Higuchi T, Reder S, Nekolla SG, Poethko T, Wester HJ, et al. Initial characterization of an $^{18}$F-labeled myocardial perfusion tracer. *J Nucl Med* 2008; **49:** 630–636. PMID: 18344426
481. Nekolla SG, Reder S, Saraste A, Higuchi T, Dzewas G, Preissel A et al. Evaluation of the novel myocardial perfusion positron-emission tomography tracer $^{18}$F-BMS-747158-02: Comparison to $^{13}$N-ammonia and validation with microspheres in a pig model. *Circulation* 2009; **119:** 2333–2342. PMID: 19380625
482. Sherif HM, Nekolla SG, Saraste A, Reder S, Yu M, Robinson S, et al. Simplified quantification of myocardial flow reserve with flurpiridaz F 18: Validation with microspheres in a pig model. *J Nucl Med* 2011; **52:** 617–624. PMID: 21441533
483. The Japanese Registry of All Cardiac and Vascular Diseases (JROAD). Annual Report 2017. Tokyo: Japanese Circulation Society (in Japanese). http://www.j-circ.or.jp/jittai_chosa/jittai_chosa2016web.pdf (accessed Dec 25, 2019).
484. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010; **56:** 1864–1894. PMID: 21087721
485. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: A report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2014; **8:** 342–358. PMID: 25301040
486. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr* 2016; **10:** 435–449. PMID: 27780758
487. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000; **36:** 1253–1260. PMID: 11028480
488. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004; **291:** 210–215. PMID: 14722147
489. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. Assessment of coronary artery disease by cardiac computed tomography: A Scientific Statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006; **114:** 1761–1791. PMID: 17015792
490. Cademartiri F, Mollet NR, Runza G, Bruining N, Hamers R, Somers P, et al. Influence of intracoronary attenuation on coronary plaque measurements using multislice computed tomography: Observations in an ex vivo model of coronary computed tomography angiography. *Eur Radiol* 2005; **15:** 1426–1431. PMID: 15750815
491. Berrington de González A, Darby S. Risk of cancer from diagnostic X-rays: Estimates for the UK and 14 other countries. *Lancet* 2004; **363:** 345–351. PMID: 15070562
492. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA* 2007; **298:** 317–323. PMID: 17635892
493. Japan Radioisotope Association. ICRP publication 73: Radiological protection and safety in medicine (in Japanese). http://www.icrp.org/docs/P73_Japanese.pdf (accessed Dec 25, 2019).
494. Japan Radioisotope Association. ICRP publication 87: Managing patient dose in computed tomography (in Japanese). http://www.icrp.org/docs/P87_Japanese.pdf (accessed Dec 25, 2019).
495. Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, et al. Cancer risks attributable to low doses of ionizing radiation: Assessing what we really know. *Proc Natl Acad Sci USA* 2003; **100:** 13761–13766. PMID: 14610281
496. Hurwitz LM, Reiman RE, Yoshizumi TT, Goodman PC, Toncheva G, Nguyen G, et al. Radiation dose from contemporary cardiothoracic multidetector CT protocols with an anthropomorphic female phantom: Implications for cancer induction. *Radiology* 2007; **245:** 742–750. PMID: 17923509
497. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K, et al. Adverse reactions to ionic and nonionic contrast media: A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990; **175:** 621–628. PMID: 2343107
498. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Matsuura K, Nakata H, et al. Full-scale investigation into adverse reaction in Japan: Risk factor analysis. The Japanese Committee on the Safety of Contrast Media. *Invest Radiol* 1991; **26**(Suppl)**:** S33–S361. PMID: 1808145
499. Ohno I, Hayashi H, Aonuma K, Horio M, Kashihara N, Okada K, et al; Japanese Society of Nephrology, Japan Radiological Society, and Japanese Circulation Society. 2018 Guidelines on use of iodinated contrast agents in patients with renal impairment. Tokyo: Tokyo Igakusha, 2018; 3–64 (in Japanese). http://www.j-circ.or.jp/guideline/pdf/2012iodine_contrast.pdf (accessed Dec 25, 2019)
500. Dangas G, Iakovou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol* 2005; **95:** 13–19. PMID: 15619387
501. Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on $\beta$-adrenergic blockers or with asthma. *Ann Intern Med* 1991; **115:** 270–276. PMID: 1677239
502. Morzycki A, Bhatia A, Murphy KJ. Adverse reactions to contrast material: A Canadian update. *Can Assoc Radiol J* 2017; **68:** 187–193. PMID: 27745988
503. Woodard PK, White RD, Abbara S, Araoz PA, Cury RC, Dorbala S, et al. ACR Appropriateness Criteria chronic chest pain: Low to intermediate probability of coronary artery disease. *J Am Coll Radiol* 2013; **10:** 329–334. PMID: 23542027
504. Akers SR, Panchal V, Ho VB, Beache GM, Brown RKJ, Ghoshhajra BB, et al; Expert Panel on Cardiac Imaging. ACR Appropriateness Criteria® chronic chest pain: High probability of coronary artery disease. *J Am Coll Radiol* 2017; **14:** S71–S80. PMID: 28473096
505. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography,

American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014; **63:** 380–406. PMID: 24355759
506. Halliburton SS, Abbara S, Chen MY, Gentry R, Mahesh M, Raff GL, et al. SCCT guidelines on radiation dose and dose-optimization strategies in cardiovascular CT. *J Cardiovasc Comput Tomogr* 2011; **5:** 198–224. PMID: 21723512
507. Chan M, Ridley L, Dunn DJ, Tian DH, Liou K, Ozdirik J, et al. A systematic review and meta-analysis of multidetector computed tomography in the assessment of coronary artery bypass grafts. *Int J Cardiol* 2016; **221:** 898–905. PMID: 27439070
508. Sheth T, Dodd JD, Hoffmann U, Abbara S, Finn A, Gold HK, et al. Coronary stent assessability by 64 slice multi-detector computed tomography. *Catheter Cardiovasc Interv* 2007; **69:** 933–938. PMID: 17421013
509. Schmitt R, Froehner S, Brunn J, Wagner M, Brunner H, Cherevatyy O, et al. Congenital anomalies of the coronary arteries: Imaging with contrast-enhanced, multidetector computed tomography. *Eur Radiol* 2005; **15:** 1110–1121. PMID: 15756551
510. Williams SV, Fihn SD, Gibbons RJ, American College of Cardiology, American Heart Association, American College of Physicians-American Society of Internal Medicine. Guidelines for the management of patients with chronic stable angina: Diagnosis and risk stratification. *Ann Intern Med* 2001; **135:** 530–547. PMID: 11578158
511. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; **97:** 1837–1847. PMID: 9603539
512. Ueshima H, Kasagi F, Kodama K, Okamura T, Hayakawa T, Okayama A, et al; NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. *Circ J* 2006; **70:** 1249–1255. PMID: 16998254
513. Wexler L, Brundage B, Crouse J, Detrano R, Fuster V, Maddahi J, et al. Coronary artery calcification: Pathophysiology, epidemiology, imaging methods, and clinical implications: A Statement for Health Professionals from the American Heart Association. *Circulation* 1996; **94:** 1175–1192. PMID: 8790070
514. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; **15:** 827–832. PMID: 2407762
515. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008; **358:** 1336–1345. PMID: 18367736
516. Yamamoto H, Ohashi N, Ishibashi K, Utsunomiya H, Kunita E, Oka T, et al. Coronary calcium score as a predictor for coronary artery disease and cardiac events in Japanese high-risk patients. *Circ J* 2011; **75:** 2424–2431. PMID: 21778594
517. Dharampal AS, Rossi A, Dedic A, Cademartiri F, Papadopoulou SL, Weustink AC, et al. Restriction of the referral of patients with stable angina for CT coronary angiography by clinical evaluation and calcium score: Impact on clinical decision making. *Eur Radiol* 2013; **23:** 2676–2686. PMID: 23774892
518. Fujimoto S, Kondo T, Yamamoto H, Yokoyama N, Tarutani Y, Takamura K, et al. Development of new risk score for pre-test probability of obstructive coronary artery disease based on coronary CT angiography. *Heart Vessels* 2015; **30:** 563–571. PMID: 24770610
519. Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, et al. Clinical indications for coronary artery calcium scoring in asymptomatic patients: Expert consensus statement from the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr* 2017; **11:** 157–168. PMID: 28283309
520. Lin JS, Evans CV, Johnson E, Redmond N, Coppola EL, Smith N. Nontraditional risk factors in cardiovascular disease risk assessment: Updated evidence report and systematic review for the US preventive services task force. *JAMA* 2018; **320:** 281–297. PMID: 29998301
521. Mahabadi AA, Berg MH, Lehmann N, Kälsch H, Bauer M, Kara K, et al. Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: The Heinz Nixdorf Recall Study. *J Am Coll Cardiol* 2013; **61:** 1388–1395. PMID: 23433560
522. Ichikawa Y, Kitagawa K, Chino S, Ishida M, Matsuoka K, Tanigawa T, et al. Adipose tissue detected by multislice computed tomography in patients after myocardial infarction. *JACC Cardiovasc Imaging* 2009; **2:** 548–555. PMID: 19442939
523. Jinzaki M, Sato K, Tanami Y, Yamada M, Anzai T, Kawamura A, et al. Diagnostic accuracy of angiographic view image for the detection of coronary artery stenoses by 64-detector row CT: A pilot study comparison with conventional post-processing methods and axial images alone. *Circ J* 2009; **73:** 691–698. PMID: 19225204
524. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS. A reporting system on patients evaluated for coronary artery disease: Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; **51**(Suppl)**:** 5–40. PMID: 1116248
525. Schroeder S, Achenbach S, Bengel F, Burgstahler C, Cademartiri F, de Feyter P, et al. Cardiac computed tomography: Indications, applications, limitations, and training requirements: Report of a Writing Group deployed by the Working Group Nuclear Cardiology and Cardiac CT of the European Society of Cardiology and the European Council of Nuclear Cardiology. *Eur Heart J* 2008; **29:** 531–556. PMID: 18084017
526. Leschka S, Alkadhi H, Plass A, Desbiolles L, Grünenfelder J, Marincek B, et al. Accuracy of MSCT coronary angiography with 64-slice technology: First experience. *Eur Heart J* 2005; **26:** 1482–1487. PMID: 15840624
527. Leber AW, Knez A, von Ziegler F, Becker A, Nikolaou K, Paul S, et al. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: A comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol* 2005; **46:** 147–154. PMID: 15992649
528. Raff GL, Gallagher MJ, O'Neill WW, Goldstein JA. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *J Am Coll Cardiol* 2005; **46:** 552–557. PMID: 16053973
529. Mollet NR, Cademartiri F, van Mieghem CA, Runza G, McFadden EP, Baks T, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation* 2005; **112:** 2318–2323. PMID: 16203914
530. Ropers D, Rixe J, Anders K, Küttner A, Baum U, Bautz W, et al. Usefulness of multidetector row spiral computed tomography with 64- × 0.6-mm collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses. *Am J Cardiol* 2006; **97:** 343–348. PMID: 16442393
531. Schuijf JD, Pundziute G, Jukema JW, Lamb HJ, van der Hoeven BL, de Roos A, et al. Diagnostic accuracy of 64-slice multislice computed tomography in the noninvasive evaluation of significant coronary artery disease. *Am J Cardiol* 2006; **98:** 145–148. PMID: 16828582
532. Ong TK, Chin SP, Liew CK, Chan WL, Seyfarth MT, Liew HB, et al. Accuracy of 64-row multidetector computed tomography in detecting coronary artery disease in 134 symptomatic patients: Influence of calcification. *Am Heart J* 2006; **151:** 1323.e1–1323.e6. PMID: 16781246
533. Ehara M, Surmely JF, Kawai M, Katoh O, Matsubara T, Terashima M, et al. Diagnostic accuracy of 64-slice computed tomography for detecting angiographically significant coronary artery stenosis in an unselected consecutive patient population: Comparison with conventional invasive angiography. *Circ J* 2006; **70:** 564–571. PMID: 16636491
534. Nikolaou K, Knez A, Rist C, Wintersperger BJ, Leber A, Johnson T, et al. Accuracy of 64-MDCT in the diagnosis of ischemic heart disease. *AJR Am J Roentgenol* 2006; **187:** 111–117. PMID: 16794164
535. Weustink AC, Meijboom WB, Mollet NR, Otsuka M, Pugliese F, van Mieghem C, et al. Reliable high-speed coronary computed tomography in symptomatic patients. *J Am Coll Cardiol* 2007; **50:** 786–794. PMID: 17707184
536. Leber AW, Johnson T, Becker A, von Ziegler F, Tittus J, Nikolaou K, et al. Diagnostic accuracy of dual-source multislice CT-coronary angiography in patients with an intermediate pretest likelihood for coronary artery disease. *Eur Heart J* 2007; **28:** 2354–2360. PMID: 17644815
537. Cheruvu C, Precious B, Naoum C, Blanke P, Ahmadi A, Soon J, et al. Long term prognostic utility of coronary CT angiography in patients with no modifiable coronary artery disease risk

factors: Results from the 5 year follow-up of the CONFIRM International Multicenter Registry. *J Cardiovasc Comput Tomogr* 2016; **10:** 22–27. PMID: 26719237
538. Meijboom WB, Van Mieghem CA, van Pelt N, Weustink A, Pugliese F, Mollet NR, et al. Comprehensive assessment of coronary artery stenoses: Computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. *J Am Coll Cardiol* 2008; **52:** 636–643. PMID: 18702967
539. Di Carli MF, Murthy VL. Cardiac PET/CT for the evaluation of known or suspected coronary artery disease. *Radiographics* 2011; **31:** 1239–1254. PMID: 21918042
540. Weigold WG, Abbara S, Achenbach S, Arbab-Zadeh A, Berman D, Carr JJ, et al. Standardized medical terminology for cardiac computed tomography: A report of the Society of Cardiovascular Computed Tomography. *J Cardiovasc Comput Tomogr* 2011; **5:** 136–144. PMID: 21640690
541. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009; **54:** 49–57. PMID: 19555840
542. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, et al. CAD-RADS™ Coronary Artery Disease–Reporting and Data System: An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. *J Cardiovasc Comput Tomogr* 2016; **10:** 269–281. PMID: 27318587
543. Yamamoto H, Kihara Y, Kitagawa T, Ohashi N, Kunita E, Iwanaga Y, et al; PREDICT Investigators. Coronary plaque characteristics in computed tomography and 2-year outcomes: The PREDICT study. *J Cardiovasc Comput Tomogr* 2018; **12:** 436–443. PMID: 30017608
544. Mochizuki T, Murase K, Higashino H, Koyama Y, Doi M, Miyagawa M, et al. Two- and three-dimensional CT ventriculography: A new application of helical CT. *AJR Am J Roentgenol* 2000; **174:** 203–208. PMID: 10628479
545. Jensen CJ, Jochims M, Hunold P, Forsting M, Barkhausen J, Sabin GV, et al. Assessment of left ventricular function and mass in dual-source computed tomography coronary angiography: Influence of beta-blockers on left ventricular function: Comparison to magnetic resonance imaging. *Eur J Radiol* 2010; **74:** 484–491. PMID: 19375878
546. Teague SD, Rissing S, Mahenthiran J, Achenbach S. Learning to interpret the extracardiac findings on coronary CT angiography examinations. *J Cardiovasc Comput Tomogr* 2012; **6:** 232–245. PMID: 22732196
547. Scholtz JE, Lu MT, Hedgire S, Meyersohn NM, Oliveira GR, Prabhakar AM, et al. Incidental pulmonary nodules in emergent coronary CT angiography for suspected acute coronary syndrome: Impact of revised 2017 Fleischner Society Guidelines. *J Cardiovasc Comput Tomogr* 2018; **12:** 28–33. PMID: 29195841
548. Gaemperli O, Bengel FM, Kaufmann PA. Cardiac hybrid imaging. *Eur Heart J* 2011; **32:** 2100–2108. PMID: 21406437
549. Pazhenkottil AP, Nkoulou RN, Ghadri JR, Herzog BA, Buechel RR, Küest SM, et al. Prognostic value of cardiac hybrid imaging integrating single-photon emission computed tomography with coronary computed tomography angiography. *Eur Heart J* 2011; **32:** 1465–1471. PMID: 21320906
550. Kurata A, Mochizuki T, Koyama Y, Haraikawa T, Suzuki J, Shigematsu Y, et al. Myocardial perfusion imaging using adenosine triphosphate stress multi-slice spiral computed tomography: Alternative to stress myocardial perfusion scintigraphy. *Circ J* 2005; **69:** 550–557. PMID: 15849441
551. Rochitte CE, George RT, Chen MY, Arbab-Zadeh A, Dewey M, Miller JM, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: The CORE320 study. *Eur Heart J* 2014; **35:** 1120–1130. PMID: 24255127
552. Tanabe Y, Kido T, Kurata A, Uetani T, Fukuyama N, Yokoi T, et al. Optimal scan time for single-phase myocardial computed tomography perfusion to detect myocardial ischemia: Derivation cohort from dynamic myocardial computed tomography perfusion. *Circ J* 2016; **80:** 2506–2512. PMID: 27795485
553. Lu M, Wang S, Sirajuddin A, Arai AE, Zhao S. Dynamic stress computed tomography myocardial perfusion for detecting myocardial ischemia: A systematic review and meta-analysis. *Int J Cardiol* 2018; **258:** 325–331. PMID: 29433968
554. Kikuchi Y, Oyama-Manabe N, Naya M, Manabe O, Tomiyama Y, Sasaki T, et al. Quantification of myocardial blood flow using dynamic 320-row multi-detector CT as compared with $^{15}O$-$H_2O$ PET. *Eur Radiol* 2014; **24:** 1547–1556. PMID: 24744200
555. Fujita M, Kitagawa K, Ito T, Shiraishi Y, Kurobe Y, Nagata M, et al. Dose reduction in dynamic CT stress myocardial perfusion imaging: Comparison of 80-kV/370-mAs and 100-kV/300-mAs protocols. *Eur Radiol* 2014; **24:** 748–755. PMID: 24272224
556. Koyama Y, Mochizuki T, Higaki J. Computed tomography assessment of myocardial perfusion, viability, and function. *J Magn Reson Imaging* 2004; **19:** 800–815. PMID: 15170785
557. Nieman K, Shapiro MD, Ferencik M, Nomura CH, Abbara S, Hoffmann U, et al. Reperfused myocardial infarction: Contrast-enhanced 64-section CT in comparison to MR imaging. *Radiology* 2008; **247:** 49–56. PMID: 18372464
558. Ko SM, Choi JW, Song MG, Shin JK, Chee HK, Chung HW, et al. Myocardial perfusion imaging using adenosine-induced stress dual-energy computed tomography of the heart: Comparison with cardiac magnetic resonance imaging and conventional coronary angiography. *Eur Radiol* 2011; **21:** 26–35. PMID: 20658242
559. Bauer RW, Kerl JM, Fischer N, Burkhard T, Larson MC, Ackermann H, et al. Dual-energy CT for the assessment of chronic myocardial infarction in patients with chronic coronary artery disease: Comparison with 3-T MRI. *AJR Am J Roentgenol* 2010; **195:** 639–646. PMID: 20729440
560. Nørgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, et al; NXT Trial Study Group. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: The NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol* 2014; **63:** 1145–1155. PMID: 24486266
561. Coenen A, Lubbers MM, Kurata A, Kono A, Dedic A, Chelu RG, et al. Fractional flow reserve computed from noninvasive CT angiography data: Diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. *Radiology* 2015; **274:** 674–683. PMID: 25322342
562. Donnelly PM, Kolossváry M, Karády J, Ball PA, Kelly S, Fitzsimons D, et al. Experience with an on-site coronary computed tomography-derived fractional flow reserve algorithm for the assessment of intermediate coronary stenoses. *Am J Cardiol* 2018; **121:** 9–13. PMID: 29103607
563. Ko BS, Cameron JD, Munnur RK, Wong DTL, Fujisawa Y, Sakaguchi T, et al. Noninvasive CT-derived FFR based on structural and fluid analysis: A comparison with invasive FFR for detection of functionally significant stenosis. *JACC Cardiovasc Imaging* 2017; **10:** 663–673. PMID: 27771399
564. Yoshioka K, Tanaka R, Muranaka K, Sasaki T, Ueda T, Chiba T, et al. Subtraction coronary CT angiography using second-generation 320-detector row CT. *Int J Cardiovasc Imaging* 2015; **31**(Suppl)**:** 51–58. PMID: 25721727
565. Wong DT, Ko BS, Cameron JD, Nerlekar N, Leung MC, Malaiapan Y, et al. Transluminal attenuation gradient in coronary computed tomography angiography is a novel noninvasive approach to the identification of functionally significant coronary artery stenosis: A comparison with fractional flow reserve. *J Am Coll Cardiol* 2013; **61:** 1271–1279. PMID: 23414792
566. Kurata A, Kono A, Sakamoto T, Kido T, Mochizuki T, Higashino H, et al. Quantification of the myocardial area at risk using coronary CT angiography and Voronoi algorithm-based myocardial segmentation. *Eur Radiol* 2015; **25:** 49–57. PMID: 25173626
567. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, et al. Fractional flow reserve: A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 1995; **92:** 3183–3193. PMID: 7586302
568. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J Koolen JJ, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996; **334:** 1703–1708. PMID: 8637515
569. De Bruyne B, Pijls NH, Bartunek J, Kulecki K, Bech JW, De Winter H, et al. Fractional flow reserve in patients with prior myocardial infarction. *Circulation* 2001; **104:** 157–162. PMID: 11447079
570. Pijls NH. Optimum guidance of complex PCI by coronary pres-

sure measurement. *Heart* 2004; **90:** 1085–1093. PMID: 15310716
571. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2017; **69:** 2212–2241. PMID: 28291663
572. Fearon WF, Bornschein B, Tonino PA, Gothe RM, Bruyne BD, Pijls NH, et al; Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) Study Investigators. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *Circulation* 2010; **122:** 2545–2550. PMID: 21126973
573. Miyoshi T, Osawa K, Ito H, Kanazawa S, Kimura T, Shiomi H, et al. Non-invasive computed fractional flow reserve from computed tomography (CT) for diagnosing coronary artery disease: Japanese results from NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *Circ J* 2015; **79:** 406–412. PMID: 25452201
574. Kim HJ, Vignon-Clementel IE, Coogan JS, Figueroa CA, Jansen KE, Taylor CA. Patient-specific modeling of blood flow and pressure in human coronary arteries. *Ann Biomed Eng* 2010; **38:** 3195–3209. PMID: 20559732
575. Taylor CA, Figueroa CA. Patient-specific modeling of cardiovascular mechanics. *Annu Rev Biomed Eng* 2009; **11:** 109–134. PMID: 19400706
576. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: Scientific basis. *J Am Coll Cardiol* 2013; **61:** 2233–2241. PMID: 23562923
577. Leipsic J, Yang TH, Thompson A, Koo BK, Mancini GB, Taylor C, et al. CT angiography (CTA) and diagnostic performance of noninvasive fractional flow reserve: Results from the Determination of Fractional Flow Reserve by Anatomic CTA (DeFACTO) study. *AJR Am J Roentgenol* 2014; **202:** 989–994. PMID: 24758651
578. Gaur S, Bezerra HG, Lassen JF, Christiansen EH, Tanaka K, Jensen JM, et al. Fractional flow reserve derived from coronary CT angiography: Variation of repeated analyses. *J Cardiovasc Comput Tomogr* 2014; **8:** 307–314. PMID: 25151923
579. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. *J Am Coll Cardiol* 2011; **58:** 1989–1997. PMID: 22032711
580. Min JK, Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, et al. Effect of image quality on diagnostic accuracy of noninvasive fractional flow reserve: Results from the prospective multicenter international DISCOVER-FLOW study. *J Cardiovasc Comput Tomogr* 2012; **6:** 191–199. PMID: 22682261
581. Min JK, Berman DS, Budoff MJ, Jaffer FA, Leipsic J, Leon MB, et al. Rationale and design of the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic AngiOgraphy) study. *J Cardiovasc Comput Tomogr* 2011; **5:** 301–309. PMID: 21930103
582. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012; **308:** 1237–1245. PMID: 22922562
583. Gaur S, Achenbach S, Leipsic J, Mauri L, Bezerra HG, Jensen JM, et al. Rationale and design of the HeartFlowNXT (HeartFlow analysis of coronary blood flow using CT angiography: NeXt sTeps) study. *J Cardiovasc Comput Tomogr* 2013; **7:** 279–288. PMID: 24268114
584. Nørgaard BL, Gaur S, Leipsic J, Ito H, Miyoshi T, Park SJ, et al. Influence of coronary calcification on the diagnostic performance of CT angiography derived FFR in coronary artery disease: A substudy of the NXT trial. *JACC Cardiovasc Imaging* 2015; **8:** 1045–1055. PMID: 26298072
585. Pontone G, Patel MR, Hlatky MA, Chiswell K, Andreini D, Norgaard BL, et al. Rationale and design of the Prospective LongitudinAl Trial of FFR$_{CT}$: Outcome and Resource IMpacts study. *Am Heart J* 2015; **170:** 438–46.e44. PMID: 26385026
586. Douglas PS, Pontone G, Hlatky MA, Patel MR, Norgaard BL, Byrne RA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: The prospective longitudinal trial of FFR(CT): Outcome and resource impacts study. *Eur Heart J* 2015; **36:** 3359–3367. PMID: 26330417
587. Hlatky MA, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, et al; PLATFORM Investigators. Quality-of-life and economic outcomes of assessing fractional flow reserve with computed tomography angiography: PLATFORM. *J Am Coll Cardiol* 2015; **66:** 2315–2323. PMID: 26475205
588. Douglas PS, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, et al; PLATFORM Investigators. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: The PLATFORM Study. *J Am Coll Cardiol* 2016; **68:** 435–445. PMID: 27470449
589. National Institute for Health and Clinical Excellence (NICE). HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. Medical Technologies Guidance [MTG32] 2017. https://www.nice.org.uk/guidance/mtg32 (accessed Dec 25, 2019). (see also https://www.nice.org.uk/guidance/mtg32/resources/heartflow-ffrct-for-estimating-fractional-flow-reserve-from-coronary-ct-angiography-pdf-64371991952581) (accessed Dec 25, 2019).
590. Kimura T, Shiomi H, Kuribayashi S, Isshiki T, Kanazawa S, Ito H, et al. Cost analysis of non-invasive fractional flow reserve derived from coronary computed tomographic angiography in Japan. *Cardiovasc Interv Ther* 2015; **30:** 38–44. PMID: 25030180
591. Japanese Circulation Society. Appropriate use criteria for FFRct: A report of the Japanese Circulation Society Appropriate Use Criteria Working Group (in Japanese). http://www.j-circ.or.jp/topics/FFRCT_tekisei_shishin.pdf (accessed Dec 25, 2019).
592. Kim KH, Doh JH, Koo BK, Min JK, Erglis A, Yang HM, et al. A novel noninvasive technology for treatment planning using virtual coronary stenting and computed tomography-derived computed fractional flow reserve. *JACC Cardiovasc Interv* 2014; **7:** 72–78. PMID: 24332418
593. Chinnaiyan KM, Akasaka T, Amano T, Bax JJ, Blanke P, De Bruyne B, et al. Rationale, design and goals of the HeartFlow assessing diagnostic value of non-invasive FFR$_{CT}$ in Coronary Care (ADVANCE) registry. *J Cardiovasc Comput Tomogr* 2017; **11:** 62–67. PMID: 28017291
594. Fairbairn TA, Nieman K, Akasaka T, Nørgaard BL, Berman DS, Raff G, et al. Real-world clinical utility and impact on clinical decision-making of coronary computed tomography angiography-derived fractional flow reserve: Lessons from the ADVANCE Registry. *Eur Heart J* 2018; **39:** 3701–3711. PMID: 30165613
595. Larose E, Ganz P, Reynolds HG, Dorbala S, Di Carli MF, Brown KA, et al. Right ventricular dysfunction assessed by cardiovascular magnetic resonance imaging predicts poor prognosis late after myocardial infarction. *J Am Coll Cardiol* 2007; **49:** 855–862. PMID: 17320743
596. Ebeling BC, Bjerner T, Hansen T, Andersson J, Lind L, Hulthe J, et al. Clinically unrecognized myocardial infarction detected at MR imaging may not be associated with atherosclerosis. *Radiology* 2007; **245:** 103–110. PMID: 17717330
597. Schwitter J, Wacker CM, van Rossum AC, Lombardi M, Al-Saadi N, Ahlstrom H, et al. MR-IMPACT: Comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicentre, multivendor, randomized trial. *Eur Heart J* 2008; **29:** 480–489. PMID: 18208849
598. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 2006; **113:** 2733–2743. PMID: 16754804
599. Lund GK, Stork A, Muellerleile K, Barmeyer AA, Bansmann MP, Knefel M, et al. Prediction of left ventricular remodeling and analysis of infarct resorption in patients with reperfused myocardial infarcts by using contrast-enhanced MR imaging. *Radiology* 2007; **245:** 95–102. PMID: 17885184

600. Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, et al. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. *J Am Coll Cardiol* 2006; **47:** 1427–1432. PMID: 16580532
601. Jahnke C, Nagel E, Gebker R, Kokocinski T, Kelle S, Manka R, et al. Prognostic value of cardiac magnetic resonance stress tests: Adenosine stress perfusion and dobutamine stress wall motion imaging. *Circulation* 2007; **115:** 1769–1776. PMID: 17353441
602. Bodi V, Sanchis J, Lopez-Lereu MP, Nunez J, Mainar L, Monmeneu JV, et al. Prognostic value of dipyridamole stress cardiovascular magnetic resonance imaging in patients with known or suspected coronary artery disease. *J Am Coll Cardiol* 2007; **50:** 1174–1179. PMID: 17868810
603. Tsao J, Kozerke S, Boesiger P, Pruessmann KP. Optimizing spatiotemporal sampling for *k-t* BLAST and *k-t* SENSE: Application to high-resolution real-time cardiac steady-state free precession. *Magn Reson Med* 2005; **53:** 1372–1382. PMID: 15906282
604. Levine GN, Gomes AS, Arai AE, Bluemke DA, Flamm SD, Kanal E, et al. Safety of magnetic resonance imaging in patients with cardiovascular devices: An American Heart Association scientific statement from the Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Council on Cardiovascular Radiology and Intervention: Endorsed by the American College of Cardiology Foundation, the North American Society for Cardiac Imaging, and the Society for Cardiovascular Magnetic Resonance. *Circulation* 2007; **116:** 2878–2891. PMID: 18025533
605. Thomzen HS, Stacul F, Almen T, Bellin MF, Bertolotto M, Bongartz G, et al; European Society of Urogenital Radiology. ESUR guidelines on contrast agents v10.0. http://www.esur.org/guidelines/ (accessed Dec 25, 2019).
606. Kanal E, Broome DR, Martin DR, Thomsen HS. Response to the FDA's May 23, 2007, nephrogenic systemic fibrosis update. *Radiology* 2008; **246:** 11–14. PMID: 17855656
607. Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology* 2007; **242:** 647–649. PMID: 17213364
608. Niemann PS, Pinho L, Balbach T, Galuschky C, Blankenhagen M, Silberbach M, et al. Anatomically oriented right ventricular volume measurements with dynamic three-dimensional echocardiography validated by 3-Tesla magnetic resonance imaging. *J Am Coll Cardiol* 2007; **50:** 1668–1676. PMID: 17950149
609. Sakuma H, Fujita N, Foo TK, Caputo GR, Nelson SJ, Hartiala J, et al. Evaluation of left ventricular volume and mass with breath-hold cine MR imaging. *Radiology* 1993; **188:** 377–380. PMID: 8327681
610. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol* 2002; **90:** 29–34. PMID: 12088775
611. Eitel I, Stiermaier T, Lange T, Rommel KP, Koschalka A, Kowallick JT, et al. Cardiac magnetic resonance myocardial feature tracking for optimized prediction of cardiovascular events following myocardial infarction. *JACC Cardiovasc Imaging* 2018; **11:** 1433–1444. PMID: 29454776
612. Amado LC, Gerber BL, Gupta SN, Rettmann DW, Szarf G, Schock R, et al. Accurate and objective infarct sizing by contrast-enhanced magnetic resonance imaging in a canine myocardial infarction model. *J Am Coll Cardiol* 2004; **44:** 2383–2389. PMID: 15607402
613. Kereiakes DJ, Teirstein PS, Sarembock IJ, Holmes DR Jr, Krucoff MW, O'Neill WW, et al. The truth and consequences of the COURAGE trial. *J Am Coll Cardiol* 2007; **50:** 1598–1603. PMID: 17936161
614. Ishida N, Sakuma H, Motoyasu M, Okinaka T, Isaka N, Nakano T, et al. Noninfarcted myocardium: Correlation between dynamic first-pass contrast-enhanced myocardial MR imaging and quantitative coronary angiography. *Radiology* 2003; **229:** 209–216. PMID: 12944596
615. Weber OM, Martin AJ, Higgins CB. Whole-heart steady-state free precession coronary artery magnetic resonance angiography. *Magn Reson Med* 2003; **50:** 1223–1228. PMID: 14648570
616. Sakuma H, Ichikawa Y, Chino S, Hirano T, Makino K, Takeda K, et al. Detection of coronary artery stenosis with whole-heart coronary magnetic resonance angiography. *J Am Coll Cardiol* 2006; **48:** 1946–1950. PMID: 17112982
617. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE, et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. *Eur Heart J* 2004; **25:** 1940–1965. PMID: 15522474
618. Bluemke DA, Achenbach S, Budoff M, Gerber TC, Gersh B, Hillis LD, et al. Noninvasive coronary artery imaging: Magnetic resonance angiography and multidetector computed tomography angiography: A Scientific Statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, and the Councils on Clinical Cardiology and Cardiovascular Disease in the Young. *Circulation* 2008; **118:** 586–606. PMID: 18586979
619. Saito Y, Sakuma H, Shibata M, Okinaka T, Isaka N, Tomemori T, et al. Assessment of coronary flow velocity reserve using fast velocity-encoded cine MRI for noninvasive detection of restenosis after coronary stent implantation. *J Cardiovasc Magn Reson* 2001; **3:** 209–214. PMID: 11816617
620. Ishida N, Sakuma H, Cruz BP, Shimono T, Tokui T, Yada IP, et al. MR flow measurement in the internal mammary artery-to-coronary artery bypass graft: Comparison with graft stenosis at radiographic angiography. *Radiology* 2001; **220:** 441–447. PMID: 11477249
621. Schwitter J, DeMarco T, Kneifel S, von Schulthess GK, Jörg MC, Arheden H, et al. Magnetic resonance-based assessment of global coronary flow and flow reserve and its relation to left ventricular functional parameters: A comparison with positron emission tomography. *Circulation* 2000; **101:** 2696–2702. PMID: 10851206
622. Shomanova Z, Florian A, Bietenbeck M, Waltenberger J, Sechtem U, Yilmaz A, et al. Diagnostic value of global myocardial perfusion reserve assessment based on coronary sinus flow measurements using cardiovascular magnetic resonance in addition to myocardial stress perfusion imaging. *Eur Heart J Cardiovasc Imaging* 2017; **18:** 851–859. PMID: 28369259
623. Indorkar R, Kwong RY, Romano S, White BE, Chia RC, Trybula M, et al. Global coronary flow reserve measured during stress cardiac magnetic resonance imaging is an independent predictor of adverse cardiovascular events. *JACC Cardiovasc Imaging* 2019; **12:** 1686–1695. PMID: 30409558
624. Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000; **343:** 1445–1453. PMID: 11078769
625. Assomull RG, Shakespeare C, Kalra PR, Lloyd G, Gulati A, Strange J, et al. Role of cardiovascular magnetic resonance as a gatekeeper to invasive coronary angiography in patients presenting with heart failure of unknown etiology. *Circulation* 2011; **124:** 1351–1360. PMID: 21900085
626. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* 2013; **309:** 896–908. PMID: 23462786
627. Takx RA, Blomberg BA, El Aidi H, Habets J, de Jong PA, Nagel E, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. *Circ Cardiovasc Imaging* 2015; **8:** e002666. PMID: 25596143
628. Lipinski MJ, McVey CM, Berger JS, Kramer CM, Salerno M. Prognostic value of stress cardiac magnetic resonance imaging in patients with known or suspected coronary artery disease: A systematic review and meta-analysis. *J Am Coll Cardiol* 2013; **62:** 826–838. PMID: 23727209
629. Greenwood JP, Herzog BA, Brown JM, Everett CC, Nixon J, Bijsterveld P, et al. Prognostic value of cardiovascular magnetic resonance and single-photon emission computed tomography in suspected coronary heart disease: Long-term follow-up of a prospective, diagnostic accuracy cohort study. *Ann Intern Med* 2016; **165:** 1–9. PMID: 27158921
630. Vincenti G, Masci PG, Monney P, Rutz T, Hugelshofer S, Gaxherri M, et al. Stress perfusion CMR in patients with known and suspected CAD: Prognostic value and optimal ischemic threshold for revascularization. *JACC Cardiovasc Imaging* 2017; **10:** 526–537. PMID: 28412420
631. Kim WY, Danias PG, Stuber M, Flamm SD, Plein S, Nagel E, et al. Coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med* 2001; **345:** 1863–1869. PMID: 11756576
632. Sakuma H, Ichikawa Y, Suzawa N, Hirano T, Makino K,

Koyama N, et al. Assessment of coronary arteries with total study time of less than 30 minutes by using whole-heart coronary MR angiography. *Radiology* 2005; **237:** 316–321. PMID: 16126921
633. Kato S, Kitagawa K, Ishida N, Ishida M, Nagata M, Ichikawa Y, et al. Assessment of coronary artery disease using magnetic resonance coronary angiography: A national multicenter trial. *J Am Coll Cardiol* 2010; **56:** 983–991. PMID: 20828652
634. Di Leo G, Fisci E, Secchi F, Alì M, Ambrogi F, Sconfienza LM, et al. Diagnostic accuracy of magnetic resonance angiography for detection of coronary artery disease: A systematic review and meta-analysis. *Eur Radiol* 2016; **26:** 3706–3718. PMID: 26662033
635. Henningsson M, Shome J, Bratis K, Vieira MS, Nagel E, Botnar RM. Diagnostic performance of image navigated coronary CMR angiography in patients with coronary artery disease. *J Cardiovasc Magn Reson* 2017; **19:** 68. PMID: 28893296
636. He Y, Pang J, Dai Q, Fan Z, An J, Li D. Diagnostic performance of self-navigated whole-heart contrast-enhanced coronary 3-T MR angiography. *Radiology* 2016; **281:** 401–408. PMID: 27192461
637. Sones FM, Shirey EK. Cine coronary arteriography. *Mod Concepts Cardiovasc Dis* 1962; **31:** 735–738. PMID: 13915182
638. Judkins MP. Selective coronary arteriography. Part I: A percutaneous transfemoral technic. *Radiology* 1967; **89:** 815–824. PMID: 6048074
639. Anne G, Gruberg L, Huber A, Nikolsky E, Grenadier E, Boulus M, et al. Traditional versus automated injection contrast system in diagnostic and percutaneous coronary interventional procedures: Comparison of the contrast volume delivered. *J Invasive Cardiol* 2004; **16:** 360–362. PMID: 15282428
640. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2012; **126:** e354–e471. PMID: 23166211
641. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2014; **130:** 1749–1767. PMID: 25070666
642. Brown BG, Bolson E, Frimer M, Dodge HT. Quantitative coronary arteriography: Estimation of dimensions, hemodynamic resistance, and atheroma mass of coronary artery lesions using the arteriogram and digital computation. *Circulation* 1977; **55:** 329–337. PMID: 832350
643. Yamagishi M, Hosokawa H, Saito S, Kanemitsu S, Chino M, Koyanagi S, et al. Coronary disease morphology and distribution determined by quantitative angiography and intravascular ultrasound: Re-evaluation in a cooperative multicenter intravascular ultrasound study (COMIUS). *Circ J* 2002; **66:** 735–740. PMID: 12197597
644. CASS principal investigators and their associates. Coronary artery surgery study (CASS): A randomized trial of coronary artery bypass surgery: Survival data. *Circulation* 1983; **68:** 939–950. PMID: 6137292
645. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX score: An angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005; **1:** 219–227. PMID: 19758907
646. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* 2013; **381:** 629–638. PMID: 23439102
647. Shiomi H, Morimoto T, Kitaguchi S, Nakagawa Y, Ishii K, Haruna Y, et al; ReACT Investigators. The ReACT trial: Randomized evaluation of routine follow-up coronary angiography after percutaneous coronary intervention trial. *JACC Cardiovasc Interv* 2017; **10:** 109–117. PMID: 28040445
648. Kennedy JW. Complications associated with cardiac catheterization and angiography. *Cathet Cardiovasc Diagn* 1982; **8:** 5–11. PMID: 7060118
649. Gersh BJ, Kronmal RA, Schaff HV, Frye RL, Ryan TJ, Myers WO, et al. Long-term (5 year) results of coronary bypass surgery in patients 65 years old or older: A report from the Coronary Artery Surgery Study. *Circulation* 1983; **68**(Suppl)**:** II190–II199. PMID: 6603283
650. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: A systematic review and meta-analysis of randomized trials. *Am Heart J* 2009; **157:** 132–140. PMID: 19081409
651. Hillis LD, Braunwald E. Coronary-artery spasm. *N Engl J Med* 1978; **299:** 695–702. PMID: 210380
652. Yasue H. Pathophysiology and treatment of coronary arterial spasm. *Chest* 1980; **78**(Suppl)**:** 216–223. PMID: 6772385
653. Okumura K, Yasue H, Matsuyama K, Goto K, Miyagi H, Ogawa H, et al. Sensitivity and specificity of intracoronary injection of acetylcholine for the induction of coronary artery spasm. *J Am Coll Cardiol* 1988; **12:** 883–888. PMID: 3047196
654. Schroeder JS, Bolen JL, Quint RA, Clark DA, Hayden WG, Higgins CB, et al. Provocation of coronary spasm with ergonovine maleate: New test with results in 57 patients undergoing coronary arteriography. *Am J Cardiol* 1977; **40:** 487–491. PMID: 910712
655. Buxton A, Goldberg S, Hirshfeld JW, Wilson J, Mann T, Williams DO, et al. Refractory ergonovine-induced coronary vasospasm: Importance of intracoronary nitroglycerin. *Am J Cardiol* 1980; **46:** 329–334. PMID: 6773407
656. Hackett D, Larkin S, Chierchia S, Davies G, Kaski JC, Maseri A. Induction of coronary artery spasm by a direct local action of ergonovine. *Circulation* 1987; **75:** 577–582. PMID: 3815770
657. Ishise S, Monji T, Takakuwa T, Kimura K, Iwainaka Y, Yamamura M, et al. Clinical application of intracoronary administration of ergonovine for detecting vasospastic angina. *Kokyu To Junkan* 1987; **35:** 191–195 (in Japanese).
658. Sueda S, Izoe Y, Kohno H, Fukuda H, Uraoka T. Need for documentation of guidelines for coronary artery spasm: An investigation by questionnaire in Japan. *Circ J* 2005; **69:** 1333–1337. PMID: 16247207
659. Ogawa H, Akasaka T, Hattori R, Inoue T, Kawashima S, Kawasuji M, et al; JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2013): Digest version. *Circ J* 2014; **78:** 2779–2801. PMID: 25273915
660. Takagi Y, Yasuda S, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, et al. Clinical characteristics and long-term prognosis of vasospastic angina patients who survived out-of-hospital cardiac arrest: Multicenter registry study of the Japanese Coronary Spasm Association. *Circ Arrhythm Electrophysiol* 2011; **4:** 295–302. PMID: 21406685
661. Takagi Y, Yasuda S, Takahashi J, Tsunoda R, Ogata Y, Seki A, et al; Japanese Coronary Spasm Association. Clinical implications of provocation tests for coronary artery spasm: Safety, arrhythmic complications, and prognostic impact: Multicentre registry study of the Japanese Coronary Spasm Association. *Eur Heart J* 2013; **34:** 258–267. PMID: 22782943
662. Sato K, Kaikita K, Nakayama N, Horio E, Yoshimura H, Ono T, et al. Coronary vasomotor response to intracoronary acetylcholine injection, clinical features, and long-term prognosis in 873 consecutive patients with coronary spasm: Analysis of a single-center study over 20 years. *J Am Heart Assoc* 2013; **2:** E000227. PMID: 23858100
663. Ishii M, Kaikita K, Sato K, Tanaka T, Sugamura K, Sakamoto K, et al. Acetylcholine-provoked coronary spasm at site of significant organic stenosis predicts poor prognosis in patients with coronary vasospastic angina. *J Am Coll Cardiol* 2015; **66:** 1105–1115. PMID: 26337988
664. Takagi Y, Takahashi J, Yasuda S, Miyata S, Tsunoda R, Ogata Y, et al; Japanese Coronary Spasm Association. Prognostic stratification of patients with vasospastic angina: A comprehensive clinical risk score developed by the Japanese Coronary Spasm Association. *J Am Coll Cardiol* 2013; **62:** 1144–1153. PMID: 23916938
665. Nosaka H, Nobuyoshi M. Coronary arterial spasm and symptomatology in ischemic and non-ischemic heart diseases: Study

of the ergonovine maleate provocative test in 3,000 consecutive patients. *J Cardiogr Suppl* 1987; **12:** 35–47 (in Japanese). PMID: 3429929
666. Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S. Circadian variation of exercise capacity in patients with Prinzmetal's variant angina: Role of exercise-induced coronary arterial spasm. *Circulation* 1979; **59:** 938–948. PMID: 428106
667. Okumura K, Yasue H, Horio Y, Takaoka K, Matsuyama K, Kugiyama K, et al. Multivessel coronary spasm in patients with variant angina: A study with intracoronary injection of acetylcholine. *Circulation* 1988; **77:** 535–542. PMID: 3342484
668. Higgins CB, Wexler L, Silverman JF, Hayden WG, Anderson WL, Schroeder JH. Spontaneously and pharmacologically provoked coronary arterial spasm in Prinzmetal variant angina. *Radiology* 1976; **119:** 521–527. PMID: 935383
669. Yamagishi M, Ito K, Tsutsui H, Miyazaki S, Goto Y, Nagaya N, et al. Lesion severity and hypercholesterolemia determine long-term prognosis of vasospastic angina treated with calcium channel antagonists. *Circ J* 2003; **67:** 1029–1035. PMID: 14639019
670. Pristipino C, Beltrame JF, Finocchiaro ML, Hattori R, Fujita M, Mongiardo R, et al. Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction. *Circulation* 2000; **101:** 1102–1108. PMID: 10715255
671. Sueda S, Kohno H. Overview of complications during pharmacological spasm provocation tests. *J Cardiol* 2016; **68:** 1–6. PMID: 27234219
672. Chin CY, Maehara A, Fall K, Mintz GS, Ali ZA. Imaging comparisons of coregistered native and stented coronary segments by high-definition 60-MHz intravascular ultrasound and optical coherence tomography. *JACC Cardiovasc Interv* 2016; **9:** 1305–1306. PMID: 27262862
673. Kume T, Uemura S. Current clinical applications of coronary optical coherence tomography. *Cardiovasc Interv Ther* 2018; **33:** 1–10. PMID: 28710605
674. Rodriguez-Granillo GA, Bruining N, Mc Fadden E, Ligthart JM, Aoki J, Regar E, et al. Geometrical validation of intravascular ultrasound radiofrequency data analysis (Virtual Histology) acquired with a 30 MHz Boston Scientific Corporation imaging catheter. *Catheter Cardiovasc Interv* 2005; **66:** 514–518. PMID: 16281299
675. Wu X, Mintz GS, Xu K, Lansky AJ, Witzenbichler B, Guagliumi G, et al. The relationship between attenuated plaque identified by intravascular ultrasound and no-reflow after stenting in acute myocardial infarction: The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv* 2011; **4:** 495–502. PMID: 21596321
676. Yamagishi M, Terashima M, Awano K, Kijima M, Nakatani S, Daikoku S, et al. Morphology of vulnerable coronary plaque: Insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol* 2000; **35:** 106–111. PMID: 10636267
677. Madder RD, Steinberg DH, Anderson RD. Multimodality direct coronary imaging with combined near-infrared spectroscopy and intravascular ultrasound: Initial US experience. *Catheter Cardiovasc Interv* 2013; **81:** 551–557. PMID: 22110009
678. Witzenbichler B, Maehara A, Weisz G, Neumann FJ, Rinaldi MJ, Metzger DC, et al. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: The assessment of dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) study. *Circulation* 2014; **129:** 463–470. PMID: 24281330
679. Steinvil A, Zhang YJ, Lee SY, Pang S, Waksman R, Chen SL, et al. Intravascular ultrasound-guided drug-eluting stent implantation: An updated meta-analysis of randomized control trials and observational studies. *Int J Cardiol* 2016; **216:** 133–139. PMID: 27153138
680. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG, et al. IVUS-XPL Investigators. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: The IVUS-XPL randomized clinical trial. *JAMA* 2015; **314:** 2155–2163. PMID: 26556051
681. Kim BK, Shin DH, Hong MK, Park HS, Rha SW, Mintz GS, et al; CTO-IVUS Study Investigators. Clinical impact of intravascular ultrasound-guided chronic total occlusion intervention with zotarolimus-eluting versus biolimus-eluting stent implantation: Randomized study. *Circ Cardiovasc Interv* 2015; **8:** E002592. PMID: 26156151
682. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes with intravascular ultrasound-guided stent implantation: A meta-analysis of randomized trials in the era of drug-eluting stents. *Circ Cardiovasc Interv* 2016; **9:** e003700. PMID: 26980883
683. Kume T, Okura H, Kawamoto T, Yamada R, Miyamoto Y, Hayashida A, et al. Assessment of the coronary calcification by optical coherence tomography. *EuroIntervention* 2011; **6:** 768–772. PMID: 21205603
684. Yabushita H, Bouma BE, Houser SL, Aretz HT, Jang IK, Schlendorf KH, et al. Characterization of human atherosclerosis by optical coherence tomography. *Circulation* 2002; **106:** 1640–1645. PMID: 12270856
685. Kubo T, Imanishi T, Takarada S, Kuroi A, Ueno S, Yamano T, et al. Assessment of culprit lesion morphology in acute myocardial infarction: Ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. *J Am Coll Cardiol* 2007; **50:** 933–939. PMID: 17765119
686. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol* 2013; **62:** 1748–1758. PMID: 23810884
687. Kobayashi Y, Okura H, Kume T, Yamada R, Kobayashi Y, Fukuhara K, et al. Impact of target lesion coronary calcification on stent expansion. *Circ J* 2014; **78:** 2209–2214. PMID: 25017740
688. Kubo T, Shimamura K, Ino Y, Yamaguchi T, Matsuo Y, Shiono Y, et al. Superficial calcium fracture after PCI as assessed by OCT. *JACC Cardiovasc Imaging* 2015; **8:** 1228–1229. PMID: 25797130
689. Gamou T, Sakata K, Matsubara T, Yasuda T, Miwa K, Inoue M, et al. Impact of thin-cap fibroatheroma on predicting deteriorated coronary flow during interventional procedures in acute as well as stable coronary syndromes: Insights from optical coherence tomography analysis. *Heart Vessels* 2015; **30:** 719–727. PMID: 25037112
690. Ueda T, Uemura S, Watanabe M, Sugawara Y, Soeda T, Okayama S, et al. Colocalization of thin-cap fibroatheroma and spotty calcification is a powerful predictor of procedure-related myocardial injury after elective coronary stent implantation. *Coron Artery Dis* 2014; **25:** 384–391. PMID: 24681754
691. Prati F, Di Vito L, Biondi-Zoccai G, Occhipinti M, La Manna A, Tamburino C, et al. Angiography alone versus angiography plus optical coherence tomography to guide decision-making during percutaneous coronary intervention: The Centro per la Lotta contro l'Infarto-Optimisation of Percutaneous Coronary Intervention (CLI-OPCI) study. *EuroIntervention* 2012; **8:** 823–829. PMID: 23034247
692. Wijns W, Shite J, Jones MR, Lee SW, Price MJ, Fabbiocchi F, et al. Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making: ILUMIEN I study. *Eur Heart J* 2015; **36:** 3346–3355. PMID: 26242713
693. Ali ZA, Maehara A, Généreux P, Shlofmitz RA, Fabbiocchi F, Nazif TM, et al; ILUMIEN III: OPTIMIZE PCI Investigators. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): A randomised controlled trial. *Lancet* 2016; **388:** 2618–2628. PMID: 27806900
694. Kubo T, Shinke T, Okamura T, Hibi K, Nakazawa G, Morino Y, et al; OPINION Investigators. Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION trial): One-year angiographic and clinical results. *Eur Heart J* 2017; **38:** 3139–3147. PMID: 29121226
695. Mizuno K, Miyamoto A, Isojima K, Kurita A, Senoo A, Arai T, et al. A serial observation of coronary thrombi in vivo by a new percutaneous transluminal coronary angioscope. *Angiology* 1992; **43:** 91–99. PMID: 1536480
696. Thieme T, Wernecke KD, Meyer R, Brandenstein E, Habedank D, Hinz A, et al. Angioscopic evaluation of atherosclerotic plaques: Validation by histomorphologic analysis and association with stable and unstable coronary syndromes. *J Am Coll Cardiol* 1996; **28:** 1–6. PMID: 8752786
697. Mizuno K, Miyamoto A, Satomura K, Kurita A, Arai T, Sakurada M, et al. Angioscopic coronary macromorphology in patients with acute coronary disorders. *Lancet* 1991; **337:** 809–812. PMID: 1672912
698. de Feyter PJ, Ozaki Y, Baptista J, Escaned J, Di Mario C, de

Jaegere PP, et al. Ischemia-related lesion characteristics in patients with stable or unstable angina: A study with intracoronary angioscopy and ultrasound. *Circulation* 1995; **92:** 1408–1413. PMID: 7664420
699. Takano M, Mizuno K, Okamatsu K, Yokoyama S, Ohba T, Sakai S. Mechanical and structural characteristics of vulnerable plaques: Analysis by coronary angioscopy and intravascular ultrasound. *J Am Coll Cardiol* 2001; **38:** 99–104. PMID: 11451303
700. Hirayama A, Saito S, Ueda Y, Takayama T, Honye J, Komatsu S, et al. Qualitative and quantitative changes in coronary plaque associated with atorvastatin therapy. *Circ J* 2009; **73:** 718–725. PMID: 19225206
701. Kodama K, Komatsu S, Ueda Y, Takayama T, Yajima J, Nanto S, et al. Stabilization and regression of coronary plaques treated with pitavastatin proven by angioscopy and intravascular ultrasound: The TOGETHAR trial. *Circ J* 2010; **74:** 1922–1928. PMID: 20625215
702. Ueda Y, Hiro T, Hirayama A, Komatsu S, Matsuoka H, Takayama T, et al; ZIPANGU Investigators. Effect of ezetimibe on stabilization and regression of intracoronary plaque: The ZIPANGU Study. *Circ J* 2017; **81:** 1611–1619. PMID: 28592751
703. Miyoshi T, Matsuoka H, Kawakami H, Dai K, Sato T, Watanabe K, et al. Assessment of second- and third-generation drug-eluting stents on chronic coronary angioscopy: Multicenter Study on Iintra-Coronary AngioScopy After Stent (MICASA) prospective data analysis. *Circ J* 2018; **82:** 1830–1835. PMID: 29607984
704. Takayama T, Hiro T, Ichikawa M, Kawano T, Saito S, Hirayama A. Association between in-stent thrombus detected by angioscopy and biomarker after drug-eluting stent implantation. *J Cardiol Jpn Ed* 2011; **6:** 293–298 (in Japanese). http://www.jcc.gr.jp/journal/backnumber/bk_jjc/pdf/J063-19.pdf (accessed Dec 25, 2019).
705. Kotani J, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, et al. Incomplete neointimal coverage of sirolimus-eluting stents: Angioscopic findings. *J Am Coll Cardiol* 2006; **47:** 2108–2111. PMID: 16697331
706. Ishihara T, Awata M, Fujita M, Watanabe T, Iida O, Ishida Y, et al. Angioscopic assessment of peri-stent contrast staining following drug-eluting stent implantation. *Circ J* 2014; **78:** 122–127. PMID: 24189464
707. Awata M, Nanto S, Uematsu M, Morozumi T, Watanabe T, Onishi T, et al. Angioscopic comparison of neointimal coverage between zotarolimus- and sirolimus-eluting stents. *J Am Coll Cardiol* 2008; **52:** 789–790. PMID: 18718430
708. Koskinas KC, Chatzizisis YS, Antoniadis AP, Giannoglou GD. Role of endothelial shear stress in stent restenosis and thrombosis: Pathophysiologic mechanisms and implications for clinical translation. *J Am Coll Cardiol* 2012; **59:** 1337–1349. PMID: 22480478
709. Ueda Y, Matsuo K, Nishimoto Y, Sugihara R, Hirata A, Nemoto T, et al. In-stent yellow plaque at 1 year after implantation is associated with future event of very late stent failure: The DESNOTE Study (Detect the Event of Very late Stent Failure From the Drug-Eluting Stent Not Well Covered by Neointima Determined by Angioscopy). *JACC Cardiovasc Interv* 2015; **8:** 814–821. PMID: 25999104
710. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* 2010; **55:** 2816–2821. PMID: 20579537
711. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 1993; **87:** 1354–1367. PMID: 8462157
712. Pijls NH, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol* 2012; **59:** 1045–1057. PMID: 22421298
713. Curzen N, Rana O, Nicholas Z, Golledge P, Zaman A, Oldroyd K, et al. Does routine pressure wire assessment influence management strategy at coronary angiography for diagnosis of chest pain?: The RIPCORD study. *Circ Cardiovasc Interv* 2014; **7:** 248–255. PMID: 24642999
714. Pijls NH, De Bruyne B, Bech GJ, Liistro F, Heyndrickx GR, Bonnier HJ, et al. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: Validation in humans. *Circulation* 2000; **102:** 2371–2377. PMID: 11067791
715. De Bruyne B, Hersbach F, Pijls NH, Bartunek J, Bech JW, Heyndrickx GR, et al. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but coronary angiography. *Circulation* 2001; **104:** 2401–2406. PMID: 11705815
716. Melikian N, De Bondt P, Tonino P, De Winter O, Wyffels E, Bartunek J, et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv* 2010; **3:** 307–314. PMID: 20298990
717. Van Belle E, Rioufol G, Pouillot C, Cuisset T, Bougrini K, Teiger E, et al; Investigators of the Registre Français de la FFR-R3F. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: Insights from a large French multicenter fractional flow reserve registry. *Circulation* 2014; **129:** 173–185. PMID: 24255062
718. Nam CW, Mangiacapra F, Entjes R, Chung IS, Sels JW, Tonino PA, et al; FAME Study Investigators. Functional SYNTAX score for risk assessment in multivessel coronary artery disease. *J Am Coll Cardiol* 2011; **58:** 1211–1218. PMID: 21903052
719. Bech GJ, Droste H, Pijls NH, De Bruyne B, Bonnier JJ, Michels HR, et al. Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease. *Heart* 2001; **86:** 547–552. PMID: 11602550
720. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation* 2009; **120:** 1505–1512. PMID: 19786633
721. Daniels DV, van't Veer M, Pijls NH, van der Horst A, Yong AS, De Bruyne B, et al. The impact of downstream coronary stenoses on fractional flow reserve assessment of intermediate left main disease. *JACC Cardiovasc Interv* 2012; **5:** 1021–1025. PMID: 23078730
722. Yong AS, Daniels D, De Bruyne B, Kim HS, Ikeno F, Lyons J, et al. Fractional flow reserve assessment of left main stenosis in the presence of downstream coronary stenoses. *Circ Cardiovasc Interv* 2013; **6:** 161–165. PMID: 23549643
723. Fearon WF, Yong AS, Lenders G, Toth GG, Dao C, Daniels DV, et al. The impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease: Human validation. *JACC Cardiovasc Interv* 2015; **8:** 398–403. PMID: 25790763
724. Aqel R, Zoghbi GJ, Hage F, Dell'Italia L, Iskandrian AE. Hemodynamic evaluation of coronary artery bypass graft lesions using fractional flow reserve. *Catheter Cardiovasc Interv* 2008; **72:** 479–485. PMID: 18814221
725. Bech GJ, Pijls NH, De Bruyne B, Peels KH, Michels HR, Bonnier HJ, et al. Usefulness of fractional flow reserve to predict clinical outcome after balloon angioplasty. *Circulation* 1999; **99:** 883–888. PMID: 10027810
726. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, et al; Fractional Flow Reserve (FFR) Post-Stent Registry Investigators. Coronary pressure measurement after stenting predicts adverse events at follow-up: A multicenter registry. *Circulation* 2002; **105:** 2950–2954. PMID: 12081986
727. Piroth Z, Toth GG, Tonino PAL, Barbato E, Aghlmandi S, Curzen N, et al. Prognostic value of fractional flow reserve measured immediately after drug-eluting stent implantation. *Circ Cardiovasc Interv* 2017; **10:** E005233. PMID: 28790165 https://doi.org/10.1161/CIRCINTERVENTIONS.116.005233 (accessed Dec 25, 2019).
728. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010; **3:** 1274–1281. PMID: 21232721
729. Kern MJ, Samady H. Current concepts of integrated coronary physiology in the catheterization laboratory. *J Am Coll Cardiol* 2010; **55:** 173–185. PMID: 20117397
730. Kern MJ, Lerman A, Bech JW, De Bruyne B, Eeckhout E, Fearon WF, et al. Physiological assessment of coronary artery disease in the cardiac catheterization laboratory: A Scientific Statement from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology. *Circulation* 2006; **114:** 1321–1341. PMID: 16940193

731. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engstrøm T, et al; FAME Study Investigators. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet* 2015; **386:** 1853–1860. PMID: 26333474
732. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014; **371:** 1208–1217. PMID: 25176289
733. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol* 2007; **49:** 2105–2111. PMID: 17531660
734. Zimmermann FM, Ferrara A, Johnson NP, van Nunen LX, Escaned J, Albertsson P, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. *Eur Heart J* 2015; **36:** 3182–3188. PMID: 26400825
735. Johnson NP, Tóth GG, Lai D, Zhu H, Açar G, Agostoni P, et al. Prognostic value of fractional flow reserve: Linking physiologic severity to clinical outcomes. *J Am Coll Cardiol* 2014; **64:** 1641–1654. PMID: 25323250
736. Ahn JM, Park DW, Shin ES, Koo BK, Nam CW, Doh JH, et al; IRIS-FFR Investigators. Fractional flow reserve and cardiac events in coronary artery disease: Data from a prospective IRIS-FFR registry (Interventional Cardiology Research Incooperation Society Fractional Flow Reserve). *Circulation* 2017; **135:** 2241–2251. PMID: 28356440
737. Barbato E, Toth GG, Johnson NP, Pijls NH, Fearon WF, Tonino PA, et al. A prospective natural history study of coronary atherosclerosis using fractional flow reserve. *J Am Coll Cardiol* 2016; **68:** 2247–2255. PMID: 27884241
738. Adjedj J, De Bruyne B, Floré V, Di Gioia G, Ferrara A, Pellicano M, et al. Significance of intermediate values of fractional flow reserve in patients with coronary artery disease. *Circulation* 2016; **133:** 502–508. PMID: 26733607
739. Kang DY, Ahn JM, Lee CH, Lee PH, Park DW, Kang SJ, et al. Deferred vs. performed revascularization for coronary stenosis with grey-zone fractional flow reserve values: Data from the IRIS-FFR registry. *Eur Heart J* 2018; **39:** 1610–1619. PMID: 29529177
740. Toth G, De Bruyne B, Casselman F, De Vroey F, Pyxaras S, Di Serafino L, et al. Fractional flow reserve-guided versus angiography-guided coronary artery bypass graft surgery. *Circulation* 2013; **128:** 1405–1411. PMID: 23985788
741. Botman CJ, Schonberger J, Koolen S, Penn O, Botman H, Dib N, et al. Does stenosis severity of native vessels influence bypass graft patency?: A prospective fractional flow reserve-guided study. *Ann Thorac Surg* 2007; **83:** 2093–2097. PMID: 17532405
742. Doh JH, Nam CW, Koo BK, Lee SY, Choi H, Namgung J, et al. Clinical relevance of poststent fractional flow reserve after drug-eluting stent implantation. *J Invasive Cardiol* 2015; **27:** 346–351. PMID: 26232010
743. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, et al. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. *Am J Cardiol* 2011; **107:** 1763–1767. PMID: 21481828
744. Baranauskas A, Peace A, Kibarskis A, Shannon J, Abraitis V, Bajoras V, et al. FFR result post PCI is suboptimal in long diffuse coronary artery disease. *EuroIntervention* 2016; **12:** 1473–1480. PMID: 27998839
745. Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P, Jüni P, et al; FAME 2 Trial Investigators. Clinical outcomes and cost-effectiveness of fractional flow reserve-guided percutaneous coronary intervention in patients with stable coronary artery disease: Three-year follow-up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). *Circulation* 2018; **137:** 480–487. PMID: 29097450
746. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: Results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol* 2012; **59:** 1392–1402. PMID: 22154731
747. Jeremias A, Maehara A, Généreux P, Asrress KN, Berry C, De Bruyne B, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: The RESOLVE study. *J Am Coll Cardiol* 2014; **63:** 1253–1261. PMID: 24211503
748. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med* 2017; **376:** 1824–1834. PMID: 28317458
749. Götberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, et al; iFR-SWEDEHEART Investigators. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med* 2017; **376:** 1813–1823. PMID: 28317438
750. van de Hoef TP, Nolte F, Damman P, Delewi R, Bax M, Chamuleau SA, et al. Diagnostic accuracy of combined intracoronary pressure and flow velocity information during baseline conditions: Adenosine-free assessment of functional coronary lesion severity. *Circ Cardiovasc Interv* 2012; **5:** 508–514. PMID: 22787017
751. Sen S, Asrress KN, Nijjer S, Petraco R, Malik IS, Foale RA, et al. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration: Results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study). *J Am Coll Cardiol* 2013; **61:** 1409–1420. PMID: 23500218
752. van de Hoef TP, Meuwissen M, Escaned J, Sen S, Petraco R, van Lavieren MA, et al. Head-to-head comparison of basal stenosis resistance index, instantaneous wave-free ratio, and fractional flow reserve: Diagnostic accuracy for stenosis-specific myocardial ischaemia. *EuroIntervention* 2015; **11:** 914–925. PMID: 25169594
753. Hwang D, Jeon KH, Lee JM, Park J, Kim CH, Tong Y, et al. Diagnostic performance of resting and hyperemic invasive physiological indices to define myocardial ischemia: Validation with $^{13}$N-ammonia positron emission tomography. *JACC Cardiovasc Interv* 2017; **10:** 751–760. PMID: 28365268
754. Petraco R, van de Hoef TP, Nijjer S, Sen S, van Lavieren MA, Foale RA, et al. Baseline instantaneous wave-free ratio as a pressure-only estimation of underlying coronary flow reserve: Results of the JUSTIFY-CFR Study (Joined Coronary Pressure and Flow Analysis to Determine Diagnostic Characteristics of Basal and Hyperemic Indices of Functional Lesion Severity-Coronary Flow Reserve). *Circ Cardiovasc Interv* 2014; **7:** 492–502. PMID: 24987048
755. Sen S, Nijjer S, Petraco R, Malik IS, Francis DP, Davies J. Instantaneous wave-free ratio: Numerically different, but diagnostically superior to FFR? Is lower always better? *J Am Coll Cardiol* 2013; **62:** 566. PMID: 23702132
756. Van't Veer M, Pijls NHJ, Hennigan B, Watkins S, Ali ZA, De Bruyne B, et al. Comparison of different diastolic resting indexes to iFR: Are they all equal? *J Am Coll Cardiol* 2017; **70:** 3088–3096. PMID: 29268922
757. Svanerud J, Ahn JM, Jeremias A, van't Veer M, Gore A, Maehara A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: The Resting Full-cycle Ratio (VALIDATE RFR) study. *EuroIntervention* 2018; **14:** 806–814. PMID: 29790478
758. Kobayashi Y, Johnson NP, Zimmermann FM, Witt N, Berry C, Jeremias A, et al; CONTRAST Study Investigators. Agreement of the resting distal to aortic coronary pressure with the instantaneous wave-free ratio. *J Am Coll Cardiol* 2017; **70:** 2105–2113. PMID: 29050557
759. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis: Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol* 1974; **33:** 87–94. PMID: 4808557
760. Danad I, Raijmakers PG, Harms HJ, Heymans MW, van Royen N, Lubberink M, et al. Impact of anatomical and functional severity of coronary atherosclerotic plaques on the transmural perfusion gradient: A [$^{15}$O]$H_2O$ PET study. *Eur Heart J* 2014; **35:** 2094–2105. PMID: 24780500
761. Kajander S, Joutsiniemi E, Saraste M, Pietilä M, Ukkonen H, Saraste A, et al. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. *Circulation* 2010; **122:** 603–613. PMID: 20660808
762. Cortigiani L, Rigo F, Gherardi S, Bovenzi F, Molinaro S, Picano E, et al. Coronary flow reserve during dipyridamole stress echocardiography predicts mortality. *JACC Cardiovasc Imaging* 2012; **5:** 1079–1085. PMID: 23153906

763. Nakatani S, Yamagishi M, Tamai J, Goto Y, Umeno T, Kawaguchi A, et al. Quantitative assessment of coronary artery stenosis by intravascular Doppler catheter technique: Application of the continuity equation. *Circulation* 1992; **85:** 1786–1791. PMID: 1572034
764. Doucette JW, Corl PD, Payne HM, Flynn AE, Goto M, Nassi M, et al. Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 1992; **85:** 1899–1911. PMID: 1572046
765. Siebes M, Verhoeff BJ, Meuwissen M, de Winter RJ, Spaan JA, Piek JJ. Single-wire pressure and flow velocity measurement to quantify coronary stenosis hemodynamics and effects of percutaneous interventions. *Circulation* 2004; **109:** 756–762. PMID: 14970112
766. De Bruyne B, Pijls NH, Smith L, Wievegg M, Heyndrickx GR. Coronary thermodilution to assess flow reserve: Experimental validation. *Circulation* 2001; **104:** 2003–2006. PMID: 11673336
767. Barbato E, Aarnoudse W, Aengevaeren WR, Werner G, Klauss V, Bojara W, et al; 'week 25 study' group. Validation of coronary flow reserve measurements by thermodilution in clinical practice. *Eur Heart J* 2004; **25:** 219–223. PMID: 14972422
768. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, et al; Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018; **250:** 16–20. PMID: 29031990
769. Baumgart D, Haude M, Liu F, Ge J, Goerge G, Erbel R. Current concepts of coronary flow reserve for clinical decision making during cardiac catheterization. *Am Heart J* 1998; **136:** 136–149. PMID: 9665231
770. Windecker S, Allemann Y, Billinger M, Pohl T, Hutter D, Orsucci T, et al. Effect of endurance training on coronary artery size and function in healthy men: An invasive followup study. *Am J Physiol Heart Circ Physiol* 2002; **282:** H2216–H2223. PMID: 12003831
771. Kern MJ, Bach RG, Mechem CJ, Caracciolo EA, Aguirre FV, Miller LW, et al. Variations in normal coronary vasodilatory reserve stratified by artery, gender, heart transplantation and coronary artery disease. *J Am Coll Cardiol* 1996; **28:** 1154–1160. PMID: 8890809
772. Nijjer SS, de Waard GA, Sen S, van de Hoef TP, Petraco R, Echavarría-Pinto M, et al. Coronary pressure and flow relationships in humans: Phasic analysis of normal and pathological vessels and the implications for stenosis assessment: A report from the Iberian-Dutch-English (IDEAL) collaborators. *Eur Heart J* 2016; **37:** 2069–2080. PMID: 26612582
773. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation* 2014; **129:** 2518–2527. PMID: 24787469
774. Cortigiani L, Rigo F, Gherardi S, Bovenzi F, Picano E, Sicari R, et al. Implication of the continuous prognostic spectrum of Doppler echocardiographic derived coronary flow reserve on left anterior descending artery. *Am J Cardiol* 2010; **105:** 158–162. PMID: 20102911
775. Serruys PW, di Mario C, Piek J, Schroeder E, Vrints C, Probst P, et al. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary balloon angioplasty: The DEBATE Study (Doppler Endpoints Balloon Angioplasty Trial Europe). *Circulation* 1997; **96:** 3369–3377. PMID: 9396429
776. Meuwissen M, Siebes M, Chamuleau SA, van Eck-Smit BL, Koch KT, de Winter RJ, et al. Hyperemic stenosis resistance index for evaluation of functional coronary lesion severity. *Circulation* 2002; **106:** 441–446. PMID: 12135943
777. Meuwissen M, Chamuleau SA, Siebes M, Schotborgh CE, Koch KT, de Winter RJ, et al. Role of variability in microvascular resistance on fractional flow reserve and coronary blood flow velocity reserve in intermediate coronary lesions. *Circulation* 2001; **103:** 184–187. PMID: 11208673
778. Fearon WF, Balsam LB, Farouque HM, Caffarelli AD, Robbins RC, Fitzgerald PJ, et al. Novel index for invasively assessing the coronary microcirculation. *Circulation* 2003; **107:** 3129–3132. PMID: 12821539
779. Echavarria-Pinto M, Escaned J, Macías E, Medina M, Gonzalo N, Petraco R, et al. Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve: A combined analysis of epicardial and microcirculatory involvement in ischemic heart disease. *Circulation* 2013; **128:** 2557–2566. PMID: 24141255
780. Haneda M, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, et al. Japanese clinical practice guideline for diabetes 2016. *Diabetol Int* 2018; **9:** 1–45. PMID: 30603347.
781. Bittner V, Bertolet M, Barraza Felix R, Farkouh ME, Goldberg S, Ramanathan KB, et al; BARI 2D Study Group. Comprehensive cardiovascular risk factor control improves survival: The BARI 2D Trial. *J Am Coll Cardiol* 2015; **66:** 765–773. PMID: 26271057
782. Pagidipati NJ, Navar AM, Pieper KS, Green JB, Bethel MA, Armstrong PW, et al; TECOS Study Group. Secondary prevention of cardiovascular disease in patients with Type 2 diabetes mellitus: International insights from the TECOS trial (Trial Evaluating Cardiovascular Outcomes With Sitagliptin). *Circulation* 2017; **136:** 1193–1203. PMID: 28626088
783. Ueki K, Sasako T, Okazaki Y, Kato M, Okahata S, Katsuyama H, et al; J-DOIT3 Study Group. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): An open-label, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; **5:** 951–964. PMID: 29079252
784. Tada H, Kawashiri MA, Yasuda K, Yamagishi M. Associations between questionnaires on lifestyle and atherosclerotic cardiovascular disease in a Japanese general population: A cross-sectional study. *PLoS One* 2018; **13:** E0208135. PMID: 30485359
785. Miura K, Nagai M, Ohkubo T. Epidemiology of hypertension in Japan: Where are we now? *Circ J* 2013; **77:** 2226–2231. PMID: 23902998
786. Fujiyoshi A, Ohkubo T, Miura K, Murakami Y, Nagasawa SY, Okamura T, et al; Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. *Hypertens Res* 2012; **35:** 947–953. PMID: 22739419
787. Kario K. Key Points of the Japanese Society of Hypertension Guidelines for the management of hypertension in 2014. *Pulse (Basel)* 2015; **3:** 35–47. PMID: 26587456
788. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; **373:** 2103–2116. PMID: 26551272
789. Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: A systematic review and network meta-analysis. *JAMA Cardiol* 2017; **2:** 775–781. PMID: 28564682
790. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; **71:** e13–e115. PMID: 29133356
791. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ* 2000; **321:** 405–412. PMID: 10938048
792. Blake DR, Meigs JB, Muller DC, Najjar SS, Andres R, Nathan DM. Impaired glucose tolerance, but not impaired fasting glucose, is associated with increased levels of coronary heart disease risk factors: Results from the Baltimore Longitudinal Study on Aging. *Diabetes* 2004; **53:** 2095–2100. PMID: 15277391
793. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, et al. Meta-analysis: Glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; **141:** 421–431. PMID: 15381515
794. Mabuchi H, Kita T, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, et al; J-LIT Study Group. Large-scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: Secondary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). *Circ J* 2002; **66:** 1096–1100. PMID: 12499612
795. Nagai R, Yamazaki T, Kitabatake A, Shimamoto K, Kikuchi K, Okumura K, et al; Japanese Coronary Artery Disease (JCAD) Study Investigators. Current status of the background of patients with coronary artery disease in Japan. *Circ J* 2006;

**70:** 1256–1262. PMID: 16998255
796. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358:** 2545–2559. PMID: 18539917
797. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358:** 2560–2572. PMID: 18539916
798. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360:** 129–139. PMID: 19092145
799. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577–1589. PMID: 18784090
800. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373:** 2117–2128. PMID: 26378978
801. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377:** 644–657. PMID: 28605608
802. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al; LEADER Steering Committee. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375:** 311–322. PMID: 27295427
803. Patel A, Barzi F, Jamrozik K, Lam TH, Ueshima H, Whitlock G, et al; Asia Pacific Cohort Studies Collaboration. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. *Circulation* 2004; **110:** 2678–2686. PMID: 15492305
804. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation* 2007; **115:** 450–458. PMID: 17190864
805. Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, et al. Serum triglycerides and risk of coronary heart disease among Japanese men and women. *Am J Epidemiol* 2001; **153:** 490–499. PMID: 11226981
806. Nagasawa SY, Okamura T, Iso H, Tamakoshi A, Yamada M, Watanabe M, et al; Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Relation between serum total cholesterol level and cardiovascular disease stratified by sex and age group: A pooled analysis of 65 594 individuals from 10 cohort studies in Japan. *J Am Heart Assoc* 2012; **1:** e001974. PMID: 23316288
807. Assmann G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk: The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis* 1996; **124**(Suppl)**:** S11–S20. PMID: 8831911
808. Kitamura A, Iso H, Naito Y, Iida M, Konishi M, Folsom AR, et al. High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men. *Circulation* 1994; **89:** 2533–2539. PMID: 8205661
809. Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, et al. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study. *Atherosclerosis* 2009; **203:** 587–592. PMID: 18783774
810. Dawber TR, Moore FE, Mann GV. Coronary heart disease in the Framingham study. *Am J Public Health Nations Health* 1957; **47:** 4–24. PMID: 13411327
811. Imano H, Noda H, Kitamura A, Sato S, Kiyama M, Sankai T, et al. Low-density lipoprotein cholesterol and risk of coronary heart disease among Japanese men and women: The Circulatory Risk in Communities Study (CIRCS). *Prev Med* 2011; **52:** 381–386. PMID: 21371493
812. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366:** 1267–1278. PMID: 16214597
813. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, et al. Early statin treatment in patients with acute coronary syndrome: Demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: The ESTABLISH Study. *Circulation* 2004; **110:** 1061–1068. PMID: 15326073
814. Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, et al; JAPAN-ACS Investigators. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: A multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). *J Am Coll Cardiol* 2009; **54:** 293–302. PMID: 19608026
815. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, et al; PRECISE–IVUS Investigators. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: The multicenter randomized controlled PRECISE-IVUS Trial. *J Am Coll Cardiol* 2015; **66:** 495–507. PMID: 26227186
816. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; **372:** 2387–2397. PMID: 26039521
817. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; **376:** 1713–1722. PMID: 28304224
818. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; **39:** 119–177. PMID: 28886621
819. Taguchi I, Iimuro S, Iwata H, Takashima H, Abe M, Amiya E, et al. High-dose versus low-dose pitavastatin in Japanese patients with stable coronary artery disease (REAL-CAD): A randomized superiority trial. *Circulation* 2018; **137:** 1997–2009. PMID: 29735587
820. Tada H, Kawashiri MA, Nomura A, Yoshimura K, Itoh H, Komuro I, et al. Serum triglycerides predict first cardiovascular events in diabetic patients with hypercholesterolemia and retinopathy. *Eur J Prev Cardiol* 2018; **25:** 1852–1860. PMID: 30160521
821. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351:** 1296–1305. PMID: 15385656
822. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: A new paradigm. *Am J Kidney Dis* 2000; **35**(Suppl)**:** S117–S131. PMID: 10766010
823. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009; **360:** 1395–1407. PMID: 19332456
824. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353:** 238–248. PMID: 16034009
825. Hou W, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: A systematic review and meta-analysis. *Eur Heart J* 2013; **34:** 1807–1817. PMID: 23470492
826. Natsuaki M, Furukawa Y, Morimoto T, Sakata R, Kimura T, CREDO-Kyoto PCI/CABG Registry Cohort-2 Investigators. Renal function and effect of statin therapy on cardiovascular outcomes in patients undergoing coronary revascularization (from the CREDO-Kyoto PCI/CABG Registry Cohort-2). *Am J Cardiol* 2012; **110:** 1568–1577. PMID: 22935527
827. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 2002;

**288:** 2421–2431. PMID: 12435255
828. Saruta T, Hayashi K, Ogihara T, Nakao K, Fukui T, Fukiyama K; CASE-J Study Group. Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: Subanalysis of the CASE-J Study. *Hypertens Res* 2009; **32:** 505–512. PMID: 19390535
829. Friedman GD, Dales LG, Ury HK. Mortality in middle-aged smokers and nonsmokers. *N Engl J Med* 1979; **300:** 213–217. PMID: 759867
830. Iso H, Date C, Yamamoto A, Toyoshima H, Watanabe Y, Kikuchi S, et al; JACC Study Group. Smoking cessation and mortality from cardiovascular disease among Japanese men and women: The JACC Study. *Am J Epidemiol* 2005; **161:** 170–179. PMID: 15632267
831. Hackshaw A, Morris JK, Boniface S, Tang JL, Milenković D. Low cigarette consumption and risk of coronary heart disease and stroke: Meta-analysis of 141 cohort studies in 55 study reports. *BMJ* 2018; **360:** j5855. PMID: 29367388
832. Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: Nearly as large as smoking. *Circulation* 2005; **111:** 2684–2698. PMID: 15911719
833. Kinjo K, Sato H, Sakata Y, Nakatani D, Mizuno H, Shimizu M, et al; Osaka Acute Coronary Insufficiency Study (OACIS) Group. Impact of smoking status on long-term mortality in patients with acute myocardial infarction. *Circ J* 2005; **69:** 7–12. PMID: 15635194
834. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: A systematic review. *JAMA* 2003; **290:** 86–97. PMID: 12837716
835. Ciruzzi M, Schargrodsky H, Rozlosnik J, Pramparo P, Delmonte H, Rudich V, et al; Argentine FRICAS (Factores de Riesgo Coronario en America del Sur) Investigators. Frequency of family history of acute myocardial infarction in patients with acute myocardial infarction. *Am J Cardiol* 1997; **80:** 122–127. PMID: 9230145
836. Leander K, Hallqvist J, Reuterwall C, Ahlbom A, de Faire U. Family history of coronary heart disease, a strong risk factor for myocardial infarction interacting with other cardiovascular risk factors: Results from the Stockholm Heart Epidemiology Program (SHEEP). *Epidemiology* 2001; **12:** 215–221. PMID: 11246583
837. Kawano H, Soejima H, Kojima S, Kitagawa A, Ogawa H, Japanese Acute Coronary Syndrome Study (JACSS) Investigators. Sex differences of risk factors for acute myocardial infarction in Japanese patients. *Circ J* 2006; **70:** 513–517. PMID: 16636482
838. Jousilahti P, Puska P, Vartiainen E, Pekkanen J, Tuomilehto J. Parental history of premature coronary heart disease: An independent risk factor of myocardial infarction. *J Clin Epidemiol* 1996; **49:** 497–503. PMID: 8636722
839. Sesso HD, Lee IM, Gaziano JM, Rexrode KM, Glynn RJ, Buring J. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation* 2001; **104:** 393–398. PMID: 11468199
840. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, Levy D, Murabito JM, Wang TJ, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: A prospective study of parents and offspring. *JAMA* 2004; **291:** 2204–2211. PMID: 15138242
841. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 2008; **359:** 1811–1821. PMID: 18946066
842. Wang J, Qin T, Chen J, Li Y, Wang L, Huang H et al. Hyperuricemia and risk of incident hypertension: A systematic review and meta-analysis of observational studies. *PLoS One* 2014; **9:** e114259. PMID: 25437867
843. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: A systematic review and meta-analysis. *Arthritis Care Res (Hoboken)* 2010; **62:** 170–180. PMID: 20191515
844. Zhang W, Iso H, Murakami Y, Miura K, Nagai M, Sugiyama D et al; EPOCH-JAPAN GROUP. Serum uric acid and mortality form cardiovascular disease: EPOCH-JAPAN study. *J Atheroscler Thromb* 2016; **23:** 692–703. PMID: 26887218
845. Costa LE, Uchôa CH, Harmon RR, Bortolotto LA, Lorenzi-Filho G, Drager LF. Potential underdiagnosis of obstructive sleep apnoea in the cardiology outpatient setting. *Heart* 2015; **101:** 1288–1292. PMID: 25897039
846. Valham F, Mooe T, Rabben T, Stenlund H, Wiklund U, Franklin KA. Increased risk of stroke in patients with coronary artery disease and sleep apnea: A 10-year follow-up. *Circulation* 2008; **118:** 955–960. PMID: 18697817
847. Lee CH, Sethi R, Li R, Ho HH, Hein T, Jim MH, et al. Obstructive sleep apnea and cardiovascular events after percutaneous coronary intervention. *Circulation* 2016; **133:** 2008–2017. PMID: 27178625
848. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, et al. CPAP versus oxygen in obstructive sleep apnea. *N Engl J Med* 2014; **370:** 2276–2285. PMID: 24918372
849. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea: The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016; **194:** 613–620. PMID: 26914592
850. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016; **375:** 919–931. PMID: 27571048
851. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, et al. Exercise-based rehabilitation for patients with coronary heart disease: Systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004; **116:** 682–692. PMID: 15121495
852. Davis MM, Taubert K, Benin AL, Brown DW, Mensah GA, Baddour LM, et al. Influenza vaccination as secondary prevention for cardiovascular disease: A Science Advisory from the American Heart Association/American College of Cardiology. *J Am Coll Cardiol* 2006; **48:** 1498–1502. PMID: 17010820
853. Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. *Eur Heart J* 2008; **29:** 1350–1358. PMID: 18187561
854. de Diego C, Vila-Córcoles A, Ochoa O, Rodriguez-Blanco T, Salsench E, Hospital I, et al; EPIVAC Study Group. Effects of annual influenza vaccination on winter mortality in elderly people with chronic heart disease. *Eur Heart J* 2009; **30:** 209–216. PMID: 18997178
855. Modin D, Jørgensen ME, Gislason G, Jensen JS, Køber L, Claggett B, et al. Influenza vaccine in heart failure: Cumulative number of vaccinations, frequency, timing, and survival: A Danish nationwide cohort study. *Circulation* 2019; **139:** 575–586. PMID: 30586760
856. Sakai M, Nakayama T, Shimbo T, Ueshima K, Kobayashi N, Izumi T, et al. Post-discharge depressive symptoms can predict quality of life in AMI survivors: A prospective cohort study in Japan. *Int J Cardiol* 2011; **146:** 379–384. PMID: 19716191
857. Shiotani I, Sato H, Kinjo K, Nakatani D, Mizuno H, Ohnishi Y, et al; Osaka Acute Coronary Insufficiency Study (OACIS) Group. Depressive symptoms predict 12-month prognosis in elderly patients with acute myocardial infarction. *J Cardiovasc Risk* 2002; **9:** 153–160. PMID: 12202838
858. Kaptein KI, de Jonge P, van den Brink RH, Korf J. Course of depressive symptoms after myocardial infarction and cardiac prognosis: A latent class analysis. *Psychosom Med* 2006; **68:** 662–668. PMID: 16987947
859. Iso H, Cui R, Date C, Kikuchi S, Tamakoshi A, JACC Study Group. C-reactive protein levels and risk of mortality from cardiovascular disease in Japanese: The JACC Study. *Atherosclerosis* 2009; **207:** 291–297. PMID: 19482283
860. Chei CL, Yamagishi K, Kitamura A, Kiyama M, Imano H, Ohira T, et al. C-reactive protein levels and risk of stroke and its subtype in Japanese: The Circulatory Risk in Communities Study (CIRCS). *Atherosclerosis* 2011; **217:** 187–193. PMID: 21444086
861. Iso H, Noda H, Ikeda A, Yamagishi K, Inoue M, Iwasaki M, et al. The impact of C-reactive protein on risk of stroke, stroke subtypes, and ischemic heart disease in middle-aged Japanese: The Japan public health center-based study. *J Atheroscler Thromb* 2012; **19:** 756–766. PMID: 22785140
862. Pfützner A, Marx N, Lübben G, Langenfeld M, Walcher D, Konrad T, et al. Improvement of cardiovascular risk markers by pioglitazone is independent from glycemic control: Results from the pioneer study. *J Am Coll Cardiol* 2005; **45:** 1925–1931. PMID: 15963388
863. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359:** 2195–2207. PMID: 18997196

864. de Lemos JA. Increasingly sensitive assays for cardiac troponins: A review. *JAMA* 2013; **309:** 2262–2269. PMID: 23736735
865. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, et al; High-STEACS investigators. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: A cohort study. *Lancet* 2015; **386:** 2481–2488. PMID: 26454362
866. Zhelev Z, Hyde C, Youngman E, Rogers M, Fleming S, Slade T, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: Systematic review and meta-analysis. *BMJ* 2015; **350:** h15. PMID: 25646632
867. Chapman AR, Lee KK, McAllister DA, Cullen L, Greenslade JH, Parsonage W, et al. Association of high-sensitivity cardiac troponin I concentration with cardiac outcomes in patients with suspected acute coronary syndrome. *JAMA* 2017; **318:** 1913–1924. PMID: 29127948, Erratum in: *JAMA* 2018; **319:** 1168. Soerensen NA [corrected to Sorensen NA]. PMID: 29127948
868. Rubini GM, Twerenbold R, Reichlin T, Wildi K, Haaf P, et al. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. *Eur Heart J* 2014; **35:** 2303–2311. PMID: 24842285
869. Cantor WJ, Newby LK, Christenson RH, Tuttle RH, Hasselblad V, Armstrong PW, et al; SYMPHONY and 2nd SYMPHONY Cardiac Markers Substudy Investigators. Prognostic significance of elevated troponin I after percutaneous coronary intervention. *J Am Coll Cardiol* 2002; **39:** 1738–1744. PMID: 12039485
870. Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR Jr, Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *J Am Coll Cardiol* 2006; **48:** 1765–1770. PMID: 17084247
871. Prasad A, Rihal CS, Lennon RJ, Singh M, Jaffe AS, Holmes DR Jr. Significance of periprocedural myonecrosis on outcomes after percutaneous coronary intervention: An analysis of preintervention and postintervention troponin T levels in 5487 patients. *Circ Cardiovasc Interv* 2008; **1:** 10–19. PMID: 20031650
872. Feldman DN, Minutello RM, Bergman G, Moussa I, Wong SC. Relation of troponin I levels following nonemergent percutaneous coronary intervention to short- and long-term outcomes. *Am J Cardiol* 2009; **104:** 1210–1215. PMID: 19840564
873. Zanchin T, Räber L, Koskinas KC, Piccolo R, Jüni P, Pilgrim T, et al. Preprocedural high-sensitivity cardiac troponin T and clinical outcomes in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention. *Circ Cardiovasc Interv* 2016; **9:** e003202. PMID: 27296200
874. Braunwald E, Domanski MJ, Fowler SE, Geller NL, Gersh BJ, Hsia J, et al; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004; **351:** 2058–2068. PMID: 15531767
875. Everett BM, Brooks MM, Vlachos HE, Chaitman BR, Frye RL, Bhatt DL, et al; BARI 2D Study Group. Troponin and cardiac events in stable ischemic heart disease and diabetes. *N Engl J Med* 2015; **373:** 610–620. PMID: 26267622
876. Rosenberg S, Elashoff MR, Beineke P, Daniels SE, Wingrove JA, Tingley WG, et al; PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) Investigators. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. *Ann Intern Med* 2010; **153:** 425–434. PMID: 20921541
877. Thomas GS, Voros S, McPherson JA, Lansky AJ, Winn ME, Bateman TM, et al. A blood-based gene expression test for obstructive coronary artery disease tested in symptomatic nondiabetic patients referred for myocardial perfusion imaging: The COMPASS study. *Circ Cardiovasc Genet* 2013; **6:** 154–162. PMID: 23418288
878. Ladapo JA, Budoff M, Sharp D, Zapien M, Huang L, Maniet B, et al. Clinical utility of a precision medicine test evaluating outpatients with suspected obstructive coronary artery disease. *Am J Med* 2017; **130:** 482.e11–482.e17. PMID: 27993573
879. Voora D, Coles A, Lee KL, Hoffmann U, Wingrove JA, Rhees B, et al. An age- and sex-specific gene expression score is associated with revascularization and coronary artery disease: Insights from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. *Am Heart J* 2017; **184:** 133–140. PMID: 28224927
880. Ripatti S, Tikkanen E, Orho-Melander M, Havulinna AS, Silander K, Sharma A, et al. A multilocus genetic risk score for coronary heart disease: Case-control and prospective cohort analyses. *Lancet* 2010; **376:** 1393–1400. PMID: 20971364
881. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield M, Devlin JJ, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: An analysis of primary and secondary prevention trials. *Lancet* 2015; **385:** 2264–2271. PMID: 25748612
882. Tikkanen E, Gustafsson S, Ingelsson E. Associations of fitness, physical activity, strength, and genetic risk with cardiovascular disease: Longitudinal analyses in the UK biobank study. *Circulation* 2018; **137:** 2583–2591. PMID: 29632216
883. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med* 2016; **375:** 2349–2358. PMID: 27959714
884. Tada H, Melander O, Louie JZ, Catanese JJ, Rowland CM, Devlin JJ, et al. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. *Eur Heart J* 2016; **37:** 561–567. PMID: 26392438
885. Antiochos P, Marques-Vidal P, McDaid A, Waeber G, Vollenweider P. Association between parental history and genetic risk scores for coronary heart disease prediction: The population-based CoLaus study. *Atherosclerosis* 2016; **244:** 59–65. PMID: 26584140
886. Mabuchi H. Half a century tales of familial hypercholesterolemia (FH) in Japan. *J Atheroscler Thromb* 2017; **24:** 189–207. PMID: 28179607
887. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: Guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. *Eur Heart J* 2013; **34:** 3478–3490. PMID: 23956253
888. Mabuchi H, Nohara A, Noguchi T, Kobayashi J, Kawashiri MA, Tada H, et al; Hokuriku FH Study Group. Molecular genetic epidemiology of homozygous familial hypercholesterolemia in the Hokuriku district of Japan. *Atherosclerosis* 2011; **214:** 404–407. PMID: 21146822
889. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, et al; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: Gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015; **36:** 2425–2437. PMID: 26009596
890. Teramoto T, Kashiwagi A, Mabuchi H, J-Lap Investigators. Status of lipid-lowering therapy prescribed based on recommendations in the 2002 report of the Japan Atherosclerosis Society Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese Adults: A study of the Japan Lipid Assessment Program (J-LAP). *Curr Ther Res Clin Exp* 2005; **66:** 80–95. PMID: 24672115
891. Ohmura H, Fukushima Y, Mizuno A, Niwa K, Kobayashi Y, Ebina T, et al; Research Committee on Primary Hyperlipidemia of the Ministry of Health and Welfare of Japan. Estimated prevalence of heterozygous familial hypercholesterolemia in patients with acute coronary syndrome. *Int Heart J* 2017; **58:** 88–94. PMID: 28123161
892. Harada T, Inagaki-Tanimura K, Nagao M, Sato Y, Sudo M, Okajima F, et al. Frequency of Achilles tendon xanthoma in patients with acute coronary syndrome. *J Atheroscler Thromb* 2017; **24:** 949–953. PMID: 28250352
893. Tada H, Kawashiri MA, Ikewaki K, Terao Y, Noguchi T, Nakanishi C, et al. Altered metabolism of low-density lipoprotein and very-low-density lipoprotein remnant in autosomal recessive hypercholesterolemia: Results from stable isotope kinetic study in vivo. *Circ Cardiovasc Genet* 2012; **5:** 35–41. PMID: 22157599
894. Harada-Shiba M, Takagi A, Miyamoto Y, Tsushima M, Ikeda Y, Yokoyama S, et al. Clinical features and genetic analysis of autosomal recessive hypercholesterolemia. *J Clin Endocrinol Metab* 2003; **88:** 2541–2547. PMID: 12788851
895. Bujo H, Takahashi K, Saito Y, Maruyama T, Yamashita S, Matsuzawa Y, et al. Clinical features of familial hypercholesterolemia in Japan in a database from 1996–1998 by the Research Committee of the Ministry of Health, Labour and Welfare of Japan. *J Atheroscler Thromb* 2004; **11:** 146–151. PMID: 15256765
896. Harada-Shiba M, Arai H, Okamura T, Yokote K, Oikawa S,

Nohara A, et al. Multicenter study to determine the diagnosis criteria of heterozygous familial hypercholesterolemia in Japan. *J Atheroscler Thromb* 2012; **19:** 1019–1026. PMID: 23095241
897. Mabuchi H, Higashikata T, Nohara A, Lu H, Yu WX, Nozue T, et al. Cutoff point separating affected and unaffected familial hypercholesterolemic patients validated by LDL-receptor gene mutants. *J Atheroscler Thromb* 2005; **12:** 35–40. PMID: 15725694
898. Harada-Shiba M, Ohta T, Ohtake A, Ogura M, Dobashi K, Nohara A, et al; Joint Working Group by Japan Pediatric Society and Japan Atherosclerosis Society for Making Guidance of Pediatric Familial Hypercholesterolemia. Guidance for pediatric familial hypercholesterolemia 2017. *J Atheroscler Thromb* 2018; **25:** 539–553. PMID: 29415907
899. Nohara A. Get the knack in diagnosis of FH: Physical findings. *Mod Physician* 2017; **37:** 1149–1153 (in Japanese).
900. Mabuchi H. *In*: Koushikessho Nyumon (Beginner's guide to hyperlipidemia). Tokyo: Bunkodo, 2005; 35–61 (in Japanese).
901. Mabuchi H, Ito S, Haba T, Ueda K, Ueda R. Discrimination of familial hypercholesterolemia and secondary hypercholesterolemia by Achilles' tendon thickness. *Atherosclerosis* 1977; **28:** 61–68. PMID: 911369
902. Tada H, Kawashiri MA, Takata M, Matsunami K, Imamura A, Matsuyama M, et al. Infantile cases of sitosterolaemia with novel mutations in the ABCG5 gene: Extreme hypercholesterolaemia is exacerbated by breastfeeding. *JIMD Rep* 2015; **21:** 115–122. PMID: 25665839
903. Tada H, Kawashiri MA, Okada H, Teramoto R, Konno T, Yoshimuta T, et al. Assessment of coronary atherosclerosis in patients with familial hypercholesterolemia by coronary computed tomography angiography. *Am J Cardiol* 2015; **115:** 724–729. PMID: 25618577
904. Mundal L, Sarancic M, Ose L, Iversen PO, Borgan JK, Veierød MB, et al. Mortality among patients with familial hypercholesterolemia: A registry-based study in Norway, 1992–2010. *J Am Heart Assoc* 2014; **3:** E001236. PMID: 25468658
905. Perak AM, Ning H, de Ferranti SD, Gooding HC, Wilkins JT, Lloyd-Jones DM, et al. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. *Circulation* 2016; **134:** 9–19. PMID: 27358432
906. Nanchen D, Gencer B, Muller O, Auer R, Aghlmandi S, Heg D, et al. Prognosis of patients with familial hypercholesterolemia after acute coronary syndromes. *Circulation* 2016; **134:** 698–709. PMID: 27462068
907. Harada-Shiba M, Arai H, Oikawa S, Ohta T, Okada T, Okamura T, et al. Guidelines for the management of familial hypercholesterolemia. *J Atheroscler Thromb* 2012; **19:** 1043–1060. PMID: 23095242
908. Japan Atherosclerosis Society. A list of core centers and specialized institutions for familil hypercholesterolemia (As of July 17, 2019) (in Japanese). http://www.j-athero.org/specialist/pdf/fh_institution.pdf (accessed Dec 25, 2019).
909. Noguchi T, Katsuda S, Kawashiri MA, Tada H, Nohara A, Inazu A, et al. The E32K variant of PCSK9 exacerbates the phenotype of familial hypercholesterolaemia by increasing PCSK9 function and concentration in the circulation. *Atherosclerosis* 2010; **210:** 166–172. PMID: 20006333
910. Tada H, Kawashiri MA, Nohara A, Inazu A, Mabuchi H, Yamagishi M, et al. Impact of clinical signs and genetic diagnosis of familial hypercholesterolaemia on the prevalence of coronary artery disease in patients with severe hypercholesterolaemia. *Eur Heart J* 2017; **38:** 1573–1579. PMID: 28159968
911. Nozue T, Higashikata T, Inazu A, Kawashiri MA, Nohara A, Kobayashi J, et al. Identification of a novel missense mutation in the sterol 27-hydroxylase gene in two Japanese patients with cerebrotendinous xanthomatosis. *Intern Med* 2010; **49:** 1127–1131. PMID: 20558929
912. Harada-Shiba M, Arai H, Ishigaki Y, Ishibashi S, Okamura T, Ogura M, et al; Working Group by Japan Atherosclerosis Society for Making Guidance of Familial Hypercholesterolemia. Guidelines for diagnosis and treatment of familial hypercholesterolemia 2017. *J Atheroscler Thromb* 2018; **25:** 751–770 (in Japanese).
913. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al. Efficacy of statins in familial hypercholesterolaemia: A long term cohort study. *BMJ* 2008; **337:** A2423. PMID: 19001495
914. Harada-Shiba M, Sugisawa T, Makino H, Abe M, Tsushima M, Yoshimasa Y, et al. Impact of statin treatment on the clinical fate of heterozygous familial hypercholesterolemia. *J Atheroscler Thromb* 2010; **17:** 667–674. PMID: 20534948
915. Raal F, Scott R, Somaratne R, Bridges I, Li G, Wasserman SM, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: The Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation* 2012; **126:** 2408–2417. PMID: 23129602
916. Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J* 2015; **36:** 2996–3003. PMID: 26330422
917. Nohara A, Ohmura H, Okazaki H, Ogura M, Kitagawa K, Koseki M, et al; Japan Atherosclerosis Society Working Group on Statement for Appropriate Use of PCSK9 Inhibitors. Statement for appropriate clinical use of PCSK9 inhibitors. *J Atheroscler Thromb* 2018; **25:** 747–750. PMID: 29899173
918. Harada-Shiba M, Ikewaki K, Nohara A, Otsubo Y, Yanagi K, Yoshida M, et al. Efficacy and safety of lomitapide in Japanese patients with homozygous familial hypercholesterolemia. *J Atheroscler Thromb* 2017; **24:** 402–411. PMID: 28154305
919. O'Gara T, Fang JC. Evaluation of the patient – The history and physical examination: An evidence-based approach. *In*: Braunwald E, editor. Heart disease: A textbook of cardiovascular medicine, 8th edn. WB Saunders, 2007; 125–130 (also see Morrow DA, Gersh BJ. Chronic coronary artery disease; 1353–1355).
920. Deedwania PC, Carbajal EV. Silent myocardial ischemia: A clinical perspective. *Arch Intern Med* 1991; **151:** 2373–2382. PMID: 1746993
921. Connolly DC, Elveback LR, Oxman HA. Coronary heart disease in residents of Rochester, Minnesota. IV: Prognostic value of the resting electrocardiogram at the time of initial diagnosis of angina pectoris. *Mayo Clin Proc* 1984; **59:** 247–250. PMID: 6708602
922. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al; ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019; **40:** 237–269. PMID: 17951284
923. Wang K, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003; **349:** 2128–2135. PMID: 14645641
924. Surawicz B, Parikh SR. Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age. *J Am Coll Cardiol* 2002; **40:** 1870–1876. PMID: 12446073
925. D'Ascenzo F, Presutti DG, Picardi E, Moretti C, Omedè P, Sciuto F, et al. Prevalence and non-invasive predictors of left main or three-vessel coronary disease: Evidence from a collaborative international meta-analysis including 22 740 patients. *Heart* 2012; **98:** 914–919. PMID: 22626899
926. Miwa K, Miyagi Y, Fujita M, Fujiki A, Sasayama S. Transient terminal U wave inversion as a more specific marker for myocardial ischemia. *Am Heart J* 1993; **125:** 981–986. PMID: 8465770
927. Morise AP. Are the American College of Cardiology/American Heart Association guidelines for exercise testing for suspected coronary artery disease correct? *Chest* 2000; **118:** 535–541. PMID: 10936152
928. Patterson RE, Horowitz SF. Importance of epidemiology and biostatistics in deciding clinical strategies for using diagnostic tests: A simplified approach using examples from coronary artery disease. *J Am Coll Cardiol* 1989; **13:** 1653–1665. PMID: 2656825
929. Goldman S, Tselos S, Cohn K. Marked depth of ST-segment depression during treadmill exercise testing: Indicator of severe coronary artery disease. *Chest* 1976; **69:** 729–733. PMID: 1277889
930. Uehara A, Kurata C, Sugi T, Mikami T, Yamazaki K, Satoh H, et al. Peak systolic blood pressure in exercise testing is associated with scintigraphic severity of myocardial ischemia in patients with exercise-induced ST-segment depression. *Jpn Circ J* 2000; **64:** 590–594. PMID: 10952155
931. Gaibazzi N, Reverberi C, Lorenzoni V, Molinaro S, Porter TR. Prognostic value of high-dose dipyridamole stress myocardial contrast perfusion echocardiography. *Circulation* 2012; **126:** 1217–1224. PMID: 22872314. Erratum in: *Circulation* 2014;

**129:** e429.
932. Gaibazzi N, Rigo F, Lorenzoni V, Molinaro S, Bartolomucci F, Reverberi C, et al. Comparative prediction of cardiac events by wall motion, wall motion plus coronary flow reserve, or myocardial perfusion analysis: A multicenter study of contrast stress echocardiography. *JACC Cardiovasc Imaging* 2013; **6:** 1–12. PMID: 23219414
933. Gurunathan S, Ahmed A, Vamvakidou A, Ramzy IS, Akhtar M, Ali A, et al. Diagnostic concordance and clinical outcomes in patients undergoing fractional flow reserve and stress echocardiography for the assessment of coronary stenosis of intermediate severity. *J Am Soc Echocardiogr* 2018; **31:** 180–186. PMID: 29246509
934. Jaarsma C, Leiner T, Bekkers SC, Crijns HJ, Wildberger JE, Nagel E, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: A meta-analysis. *J Am Coll Cardiol* 2012; **59:** 1719–1728. PMID: 22554604
935. Yang Z, Zheng H, Zhou T, Yang LF, Hu XF, Peng ZH, et al. Diagnostic performance of myocardial perfusion imaging with SPECT, CT and MR compared to fractional flow reserve as reference standard. *Int J Cardiol* 2015; **190:** 103–105. PMID: 25920018
936. Buechel RR, Kaufmann BA, Tobler D, Wild D, Zellweger MJ. Non-invasive nuclear myocardial perfusion imaging improves the diagnostic yield of invasive coronary angiography. *Eur Heart J Cardiovasc Imaging* 2015; **16:** 842–847. PMID: 25914037
937. Hussain ST, Paul M, Morton G, Schuster A, Chiribiri A, Perera D G, et al. Correlation of fractional flow reserve with ischemic burden measured by cardiovascular magnetic resonance perfusion imaging. *Am J Cardiol* 2017; **120:** 1913–1919. PMID: 29050683
938. Li M, Zhou T, Yang LF, Peng ZH, Ding J, Sun G. Diagnostic accuracy of myocardial magnetic resonance perfusion to diagnose ischemic stenosis with fractional flow reserve as reference: Systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2014; **7:** 1098–1105. PMID: 25306540
939. Dweck MR, Williams MC, Moss AJ, Newby DE, Fayad ZA. Computed tomography and cardiac magnetic resonance in ischemic heart disease. *J Am Coll Cardiol* 2016; **68:** 2201–2216. PMID: 27855810
940. Foy AJ, Dhruva SS, Peterson B, Mandrola JM, Morgan DJ, Redberg RF. Coronary computed tomography angiography vs functional stress testing for patients with suspected coronary artery disease: A systematic review and meta-analysis. *JAMA Intern Med* 2017; **177:** 1623–1631. PMID: 28973101
941. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: Results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008; **52:** 1724–1732. PMID: 19007693
942. Nakahara T, Iwabuchi Y, Murakami K. Diagnostic Performance of 3D bull's eye display of SPECT and coronary CTA fusion. *JACC Cardiovasc Imaging* 2016; **9:** 703–711. PMID: 27209105
943. Yasue H, Mizuno Y, Harada E, Itoh T. Clinical findings, underlying mechanisms, and treatment of vasospastic angina: Based on the latest knowledge. *Nihon Iji Shinpou* 2005; **4258:** 12–17 (in Japanese).
944. Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. I: A variant form of angina pectoris; preliminary report. *Am J Med* 1959; **27:** 375–388. PMID: 14434946
945. Nakamura M, Takeshita A, Nose Y. Clinical characteristics associated with myocardial infarction, arrhythmias, and sudden death in patients with vasospastic angina. *Circulation* 1987; **75:** 1110–1116. PMID: 3568322
946. Previtali M, Ardissino D, Barberis P, Panciroli C, Chimienti M, Salerno JA. Hyperventilation and ergonovine tests in Prinzmetal's variant angina pectoris in men. *Am J Cardiol* 1989; **63:** 17–20. PMID: 2909157
947. Girotti LA, Crosatto JR, Messuti H, Kaski JC, Dyszel E, Rivas CA, et al. The hyperventilation test as a method for developing successful therapy in Prinzmetal's angina. *Am J Cardiol* 1982; **49:** 834–841. PMID: 7064832
948. Yasue H, Horio Y, Nakamura N, Fujii H, Imoto N, Sonoda R, et al. Induction of coronary artery spasm by acetylcholine in patients with variant angina: Possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. *Circulation* 1986; **74:** 955–963. PMID: 3769179
949. Nakamura N, Akasaka T. Progress in invasive imaging disgnosis. *Nihon Naika Gakkai Zasshi* 2009; **98:** 280–288 (in Japanese).
950. White CW, Wright CB, Doty DB, Hiratza LF, Eastham CL, Harrison DG, et al. Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med* 1984; **310:** 819–824. PMID: 6700670
951. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988; **78:** 1157–1166. PMID: 3180375
952. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; **92:** 657–671. PMID: 7634481
953. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987; **316:** 1371–1375. PMID: 3574413
954. Mintz GS, Painter JA, Pichard AD, Kent KM, Satler LF, Popma JJ, et al. Atherosclerosis in angiographically "normal" coronary artery reference segments: An intravascular ultrasound study with clinical correlations. *J Am Coll Cardiol* 1995; **25:** 1479–1485. PMID: 7759694
955. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: Outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation* 1997; **95:** 2037–2043. PMID: 9133513
956. Muranaka A, Tsuchihashi K, Hase M. Silent myocardial ischemia. Circulation Syndrome (II). *Nihon Rinshyo* 2007; **28**(Suppl V)**:** 245–248 (in Japanese).
957. Ehara M. Practical use of multi slice computed tomography (MSCT) as a routine test tool-outcomes and problems in daily clinical practice. *Nihon Naika Gakkai Zasshi* 2009; **98:** 289–298 (in Japanese). https://www.jstage.jst.go.jp/article/naika/98/2/98_289/_pdf/-char/ja (accessed Dec 25, 2019).
958. Marano R, Liguori C, Rinaldi P, Storto ML, Politi MA, Savino G, et al. Coronary artery bypass grafts and MDCT imaging: What to know and what to look for. *Eur Radiol* 2007; **17:** 3166–3178. PMID: 17874112
959. Schroeder S, Kopp AF, Baumbach A, Meisner C, Kuettner A, Georg C, et al. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. *J Am Coll Cardiol* 2001; **37:** 1430–1435. PMID: 11300457
960. Achenbach S, Ropers D, Hoffmann U, MacNeill B, Baum U, Pohle K, et al. Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. *J Am Coll Cardiol* 2004; **43:** 842–847. PMID: 14998627
961. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: A prospective, multicenter, multivendor study. *J Am Coll Cardiol* 2008; **52:** 2135–2144. PMID: 19095130
962. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008; **359:** 2324–2336. PMID: 19038879
963. Kuribayashi Y. Coronary artery CT: Progress, current status, and future prospects. *Shinzo* 2006; **38:** 886–896 (in Japanese). https://www.jstage.jst.go.jp/article/shinzo1969/38/9/38_886/_pdf/-char/ja (accessed Dec 25, 2019).
964. Mollet NR, Hoye A, Lemos PA, Cademartiri F, Sianos G, McFadden EP, et al. Value of preprocedure multislice computed tomographic coronary angiography to predict the outcome of percutaneous recanalization of chronic total occlusions. *Am J Cardiol* 2005; **95:** 240–243. PMID: 15642558
965. Mitsutake R, Miura S, Nishikawa H, Saku K. Usefulness of the evaluation of stent fracture by 64-multi-detector row computed tomography. *J Cardiol* 2008; **51:** 135–138. PMID: 18522787
966. O'Rourke RA, Brundage BH, Froelicher VF, Greenland P, Grundy SM, Hachamovitch R, et al. American College of Cardiology/American Heart Association Expert Consensus document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *Circulation* 2000; **102:**

126–140. PMID: 10880426
967. Miura T. Coronary artery calcification: Circulation syndrome (II). *Nihon Rinshyo* 2007; **28**(Suppl V)**:** 55–58 (in Japanese).
968. Haberl R, Becker A, Leber A, Knez A, Becker C, Lang C, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: Results of 1,764 patients. *J Am Coll Cardiol* 2001; **37:** 451–457. PMID: 11216962
969. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol* 2007; **49:** 378–402. PMID: 17239724
970. Sekikawa A, Ueshima H, Zaky WR, Kadowaki T, Edmundowicz D, Okamura T, et al. Much lower prevalence of coronary calcium detected by electron-beam computed tomography among men aged 40–49 in Japan than in the US, despite a less favorable profile of major risk factors. *Int J Epidemiol* 2005; **34:** 173–179. PMID: 15563587
971. Mitsutake R, Niimura H, Miura S, Zhang B, Iwata A, Nishikawa H, et al. Clinical significance of the coronary calcification score by multidetector row computed tomography for the evaluation of coronary stenosis in Japanese patients. *Circ J* 2006; **70:** 1122–1127. PMID: 16936422
972. Gottlieb I, Miller JM, Arbab-Zadeh A, Dewey M, Clouse ME, Sara L, et al. The absence of coronary calcification does not exclude obstructive coronary artery disease or the need for revascularization in patients referred for conventional coronary angiography. *J Am Coll Cardiol* 2010; **55:** 627–634. PMID: 20170786
973. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007; **50:** 319–326. PMID: 17659199
974. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: Results from the ROMICAT-II trial. *J Am Coll Cardiol* 2014; **64:** 684–692. PMID: 25125300
975. Otsuka K, Fukuda S, Tanaka A, Nakanishi K, Taguchi H, Yoshikawa J, et al. Napkin-ring sign on coronary CT angiography for the prediction of acute coronary syndrome. *JACC Cardiovasc Imaging* 2013; **6:** 448–457. PMID: 23498679
976. Ishida M, Kato S, Sakuma H. Cardiac MRI in ischemic heart disease. *Circ J* 2009; **73:** 1577–1588. PMID: 19667487
977. Japan Radiological Society, Japanese Society for Magnetic Resonance in Medicine, and Japanese Heart Rhythm Society. Requirements for magnetic resonance imaging in patients with magnetic resonance-compatible cardiac implantable electronic devices. 2014 (in Japanese). http://www.jsmrm.jp/modules/other/index.php?content_id=5 (accessed Dec 25, 2019).
978. Jahnke C, Paetsch I, Nehrke K, Schnackenburg B, Gebker R, Fleck E, et al. Rapid and complete coronary arterial tree visualization with magnetic resonance imaging: Feasibility and diagnostic performance. *Eur Heart J* 2005; **26:** 2313–2319. PMID: 15987709
979. Kawasaki T, Koga S, Koga N, Noguchi T, Tanaka H, Koga H, et al. Characterization of hyperintense plaque with noncontrast T1-weighted cardiac magnetic resonance coronary plaque imaging: Comparison with multislice computed tomography and intravascular ultrasound. J*ACC Cardiovasc Imaging* 2009; **2:** 720–728. PMID: 19520342
980. Noguchi T, Kawasaki T, Tanaka A, Yasuda S, Goto Y, Ishihara M, et al. High-intensity signals in coronary plaques on noncontrast T1-weighted magnetic resonance imaging as a novel determinant of coronary events. *J Am Coll Cardiol* 2014; **63:** 989–999. PMID: 24345595
981. Noguchi T, Tanaka A, Kawasaki T, Goto Y, Morita Y, Asaumi Y et al. Effect of intensive statin therapy on coronary high-intensity plaques detected by noncontrast T1-weighted imaging: The AQUAMARINE Pilot Study. *J Am Coll Cardiol* 2015; **66:** 245–256. PMID: 26184618
982. Ishida M, Sakuma H, Kato N, Ishida N, Kitagawa K, Shimono T, et al. Contrast-enhanced MR imaging for evaluation of coronary artery disease before elective repair of aortic aneurysm. *Radiology* 2005; **237:** 458–464. PMID: 16170013
983. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: Summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation* 2003; **108:** 1146–1162. PMID: 12952829
984. Hozumi T. Progress in echocardiographic diagnosis. *Nihon Naika Gakkai Zasshi* 2009; **98:** 263–271 (in Japanese). https://www.jstage.jst.go.jp/article/naika/98/2/98_263/_pdf/-char/ja (accessed Dec 25, 2019).
985. Gibbons RJ. Noninvasive diagnosis and prognosis assessment in chronic coronary artery disease: Stress testing with and without imaging perspective. *Circ Cardiovasc Imaging* 2008; **1:** 257–269. PMID: 19808550
986. Sawada SG, Segar DS, Ryan T, Brown SE, Dohan AM, Williams R, et al. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991; **83:** 1605–1614. PMID: 1673646
987. Geleijnse ML, Fioretti PM, Roelandt JR. Methodology, feasibility, safety and diagnostic accuracy of dobutamine stress echocardiography. *J Am Coll Cardiol* 1997; **30:** 595–606. PMID: 9283514
988. Marcovitz PA, Armstrong WF. Accuracy of dobutamine stress echocardiography in detecting coronary artery disease. *Am J Cardiol* 1992; **69:** 1269–1273. PMID: 1585858
989. Armstrong WF, Pellikka PA, Ryan T, Crouse L, Zoghbi WA. Stress echocardiography: Recommendations for performance and interpretation of stress echocardiography. Stress Echocardiography Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 1998; **11:** 97–104. PMID: 9487482
990. Matsumura Y, Hozumi T, Watanabe H, Fujimoto K, Sugioka K, Takemoto Y, et al. Cut-off value of coronary flow velocity reserve by transthoracic Doppler echocardiography for diagnosis of significant left anterior descending artery stenosis in patients with coronary risk factors. *Am J Cardiol* 2003; **92:** 1389–1393. PMID: 14675571
991. Murata E, Hozumi T, Matsumura Y, Fujimoto K, Sugioka K, Takemoto Y, et al. Coronary flow velocity reserve measurement in three major coronary arteries using transthoracic Doppler echocardiography. *Echocardiography* 2006; **23:** 279–286. PMID: 16640704
992. Blankenhorn DH, Azen SP, Kramsch DM, Mack WJ, Cashin-Hemphill L, Hodis HN, et al; MARS Research Group. Coronary angiographic changes with lovastatin therapy: The Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med* 1993; **119:** 969–976. PMID: 8214993
993. Topol EJ, Nissen SE. Our preoccupation with coronary luminology: The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995; **92:** 2333–2342. PMID: 7554219
994. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Chuang YC, et al. Limitations of angiography in the assessment of plaque distribution in coronary artery disease: A systematic study of target lesion eccentricity in 1446 lesions. *Circulation* 1996; **93:** 924–931. PMID: 8598083
995. Nakamura M, Yamagishi M, Ueno T, Hara K, Ishiwata S, Itoh T, et al. Modification of treatment strategy after FFR measurement: CVIT-DEFER registry. *Cardiovasc Interv Ther* 2015; **30:** 12–21. PMID: 24816634
996. Zaret BL, Wackers FJ, Terrin ML, Forman SA, Williams DO, Knatterud GL, et al; The TIMI Study Group. Value of radionuclide rest and exercise left ventricular ejection fraction in assessing survival of patients after thrombolytic therapy for acute myocardial infarction: Results of Thrombolysis in Myocardial Infarction (TIMI) phase II study. *J Am Coll Cardiol* 1995; **26:** 73–79. PMID: 7797778
997. Rouleau JL, Talajic M, Sussex B, Potvin L, Warnica W, Davies RF, et al. Myocardial infarction patients in the 1990s: Their risk factors, stratification and survival in Canada: The Canadian Assessment of Myocardial Infarction (CAMI) Study. *J Am Coll Cardiol* 1996; **27:** 1119–1127. PMID: 8609330
998. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. *Lancet*

2003; **361:** 13–20. PMID: 12517460
999. Topol E, Califf R, Van de Werf F, Armstrong PW, Aylward P, Barbash G, et al; The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; **329:** 673–682. PMID: 8204123
1000. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, et al; Stent Primary Angioplasty in Myocardial Infarction Study Group. Coronary angioplasty with or without stent implantation for acute myocardial infarction. *N Engl J Med* 1999; **341:** 1949–1956. PMID: 10607811
1001. Itoh T. Pre and post myocardial infarction angina: Circulation syndrome (II). *Nihon Rinshyo* 2007; **28**(Suppl V)**:** 173–177 (in Japanese).
1002. Cohn PF. Silent myocardial ischemia. *Ann Intern Med* 1988; **109:** 312–317. PMID: 3293494
1003. Takano T, Ogawa S, Kasanuki H, Kimura K, Goto Y, Sumiyoshi T, et al; JCS Joint Working Group. Guidelines for the management of patients with ST-elevation myocardial infarction (JCS 2008). *Circ J* 2008; **72**(Suppl IV)**:** 1347–1442 (in Japanese). www.j-circ.or.jp/guideline/pdf/JCS2008_takano_d.pdf (accessed Dec 25, 2019).
1004. Ueda Y, Asakura M, Yamaguchi O, Hirayama A, Hori M, Kodama K. Extensive development of vulnerable plaques as a pan-coronary process in patients with myocardial infarction: An angioscopic study. *J Am Coll Cardiol* 2001; **37:** 1284–1288. PMID: 11300436
1005. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: A call for new definitions and risk assessment strategies: Part I. *Circulation* 2003; **108:** 1664–1672. PMID: 14530185
1006. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998; **97:** 765–772. PMID: 9498540
1007. Gerber BL, Belge B, Legros GJ, Lim P, Poncelet A, Pasquet A, et al. Characterization of acute and chronic myocardial infarcts by multidetector computed tomography: Comparison with contrast-enhanced magnetic resonance. *Circulation* 2006; **113:** 823–833. PMID: 16461822
1008. Mintz GS, Douek P, Pichard AD, Kent KM, Satler LF, Popma JJ, et al. Target lesion calcification in coronary artery disease: An intravascular ultrasound study. *J Am Coll Cardiol* 1992; **20:** 1149–1155. PMID: 1401615
1009. Fitzgerald PJ, St Goar FG, Connolly AJ, Pinto FJ, Billingham ME, Popp RL, et al. Intravascular ultrasound imaging of coronary arteries. Is three layers the norm? *Circulation* 1992; **86:** 154–158. PMID: 1617768
1010. Kubo T, Tanaka A, Ino Y, Kitabata H, Shiono Y, Akasaka T. Assessment of coronary atherosclerosis using optical coherence tomography. *J Atheroscler Thromb* 2014; **21:** 895–903. PMID: 25069815
1011. Mintz GS. Clinical utility of intravascular imaging and physiology in coronary artery disease. *J Am Coll Cardiol* 2014; **64:** 207–222. PMID: 24530669
1012. Jang JS, Song YJ, Kang W, Jin HY, Seo JS, Yang TH, et al. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: A meta-analysis. *JACC Cardiovasc Interv* 2014; **7:** 233–243. PMID: 24529934
1013. Ahn JM, Kang SJ, Yoon SH, Park HW, Kang SM, Lee JY, et al. Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies. *Am J Cardiol* 2014; **113:** 1338–1347. PMID: 24685326
1014. Okabe T, Mintz GS, Buch AN, Roy P, Hong YJ, Smith KA, et al. Intravascular ultrasound parameters associated with stent thrombosis after drug-eluting stent deployment. *Am J Cardiol* 2007; **100:** 615–620. PMID: 17697816
1015. Doi H, Maehara A, Mintz GS, Yu A, Wang H, Mandinov L, et al. Impact of post-intervention minimal stent area on 9-month follow-up patency of paclitaxel-eluting stents: An integrated intravascular ultrasound analysis from the TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trials. *JACC Cardiovasc Interv* 2009; **2:** 1269–1275. PMID: 20129555
1016. Sousa JE, Costa MA, Abizaid A, Abizaid AS, Feres F, Pinto IM, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: A quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation* 2001; **103:** 192–195. PMID: 11208675
1017. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349:** 1315–1323. PMID: 14523139
1018. Schampaert E, Cohen EA, Schlüter M, Reeves F, Traboulsi M, Title LM, et al; C-SIRIUS Investigators. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004; **43:** 1110–1115. PMID: 15028375
1019. Urban P, Gershlick AH, Guagliumi G, Guyon P, Lotan C, Schofer J, et al; e-Cypher Investigators. Safety of coronary sirolimus-eluting stents in daily clinical practice: One-year follow-up of the e-Cypher registry. *Circulation* 2006; **113:** 1434–1441. PMID: 16534015
1020. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al; TAXUS-IV Investigators. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: The TAXUS-IV trial. *Circulation* 2004; **109:** 1942–1947. PMID: 15078803
1021. Ong AT, Serruys PW, Aoki J, Hoye A, van Mieghem CA, Rodriguez-Granillo GA, et al. The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: One-year results of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. *J Am Coll Cardiol* 2005; **45:** 1135–1141. PMID: 15808774
1022. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: Drug-eluting stents: Part II. *Circulation* 2003; **107:** 2383–2389. PMID: 12742968
1023. Kiat H, Berman DS, Maddahi J, De Yang L, Van Train K, Rozanski A, et al. Late reversibility of tomographic myocardial thallium-201 defects: An accurate marker of myocardial viability. *J Am Coll Cardiol* 1988; **12:** 1456–1463. PMID: 3263995
1024. Ghosh N, Rimoldi OE, Beanlands RS, Camici PG. Assessment of myocardial ischaemia and viability: Role of positron emission tomography. *Eur Heart J* 2010; **31:** 2984–2995. PMID: 20965888
1025. Braunwald E, Kloner RA. The stunned myocardium: Prolonged, postischemic ventricular dysfunction. *Circulation* 1982; **66:** 1146–1149. PMID: 6754130
1026. Vanoverschelde JL, Wijns W, Depré C, Essamri B, Heyndrickx GR, Borgers M, et al. Mechanisms of chronic regional postischemic dysfunction in humans: New insights from the study of noninfarcted collateral-dependent myocardium. *Circulation* 1993; **87:** 1513–1523. PMID: 8491006
1027. Shen YT, Vatner SF. Mechanism of impaired myocardial function during progressive coronary stenosis in conscious pigs: Hibernation versus stunning? *Circ Res* 1995; **76:** 479–488. PMID: 7859393
1028. Piérard LA, Lancellotti P, Kulbertus HE. ST-segment elevation during dobutamine stress testing predicts functional recovery after acute myocardial infarction. *Am Heart J* 1999; **137:** 500–511. PMID: 10047633
1029. Nakano A, Lee JD, Shimizu H, Tsuchida T, Yonekura Y, Ishii Y, et al. Reciprocal ST-segment depression associated with exercise-induced ST-segment elevation indicates residual viability after myocardial infarction. *J Am Coll Cardiol* 1999; **33:** 620–626. PMID: 10080460
1030. Ono S. The clinical studies of relationship between ischemia-induced negative U wave and myocardial viability. *Nihon Naika Gakkai Zasshi* 1986; **75:** 495–506 (in Japanese). PMID: 3734538
1031. Schneider CA, Voth E, Baer FM, Horst M, Wagner R, Sechtem U. QT dispersion is determined by the extent of viable myocardium in patients with chronic Q-wave myocardial infarction. *Circulation* 1997; **96:** 3913–3920. PMID: 9403615
1032. Arnold JM, Braunwald E, Sandor T, Kloner RA. Inotropic stimulation of reperfused myocardium with dopamine: Effects on infarct size and myocardial function. *J Am Coll Cardiol* 1985; **6:** 1026–1034. PMID: 4045027
1033. Sicari R, Varga A, Picano E, Borges AC, Gimelli A, Marzullo P. Comparison of combination of dipyridamole and dobutamine during echocardiography with thallium scintigraphy to improve viability detection. *Am J Cardiol* 1999; **83:** 6–10. PMID: 10073776
1034. Bonow RO. Myocardial viability and prognosis in patients with

ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2002; **39:** 1159–1162. PMID: 11923040
1035. Smart SC, Sawada S, Ryan T, Segar D, Atherton L, Berkovitz K, et al. Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction. *Circulation* 1993; **88:** 405–415. PMID: 8339404 https://doi.org/10.1161/01.CIR.88.2.405 (accessed Dec 25, 2019).
1036. Fukai T, Koyanagi S, Tashiro H, Ichiki T, Tsutsui H, Matsumoto T, et al. Adenosine triphosphate stress echocardiography in the detection of myocardial ischemia. *Am J Card Imaging* 1995; **9:** 237–244. PMID: 8680139
1037. Charney R, Schwinger ME, Chun J, Cohen MV, Nanna M, Menegus MA, et al. Dobutamine echocardiography and resting-redistribution thallium-201 scintigraphy predicts recovery of hibernating myocardium after coronary revascularization. *Am Heart J* 1994; **128:** 864–869. PMID: 7942476
1038. Hirano Y, Habu H, Miyazaki T, Yamamoto T, Ikawa H, Sasaki T, et al. Diagnosis of ischemic heart disease by dipyridamole-stress two-dimensional echocardiography. *J Cardiol* 1994; **24:** 9–16 (in Japanese).
1039. Marzullo P, Parodi O, Reisenhofer B, Sambuceti G, Picano E, Distante A, et al. Value of rest thallium-201/technetium-99m sestamibi scans and dobutamine echocardiography for detecting myocardial viability. *Am J Cardiol* 1993; **71:** 166–172. PMID: 8421978
1040. Watada H, Ito H, Oh H, Masuyama T, Aburaya M, Hori M, et al. Dobutamine stress echocardiography predicts reversible dysfunction and quantitates the extent of irreversibly damaged myocardium after reperfusion of anterior myocardial infarction. *J Am Coll Cardiol* 1994; **24:** 624–630. PMID: 8077530
1041. Arnese M, Cornel JH, Salustri A, Maat A, Elhendy A, Reijs AE, et al. Prediction of improvement of regional left ventricular function after surgical revascularization: A comparison of low-dose dobutamine echocardiography with $^{201}$Tl single-photon emission computed tomography. *Circulation* 1995; **91:** 2748–2752. PMID: 7758180
1042. Haque T, Furukawa T, Takahashi M, Kinoshita M. Identification of hibernating myocardium by dobutamine stress echocardiography: Comparison with thallium-201 reinjection imaging. *Am Heart J* 1995; **130:** 553–563. PMID: 7661075
1043. Krahwinkel W, Ketteler T, Gödke J, Wolfertz J, Ulbricht LJ, Krakau I, et al. Dobutamine stress echocardiography. *Eur Heart J* 1997; **18**(Suppl)**:** D9–D15. PMID: 9183605
1044. Abdelgawwad IM, Al Hawary AA, Kamal HM, Al Maghawry LM. Prediction of left ventricular contractile recovery using tissue Doppler strain and strain rate measurements at rest in patients undergoing percutaneous coronary intervention. *Int J Cardiovasc Imaging* 2017; **33:** 643–651. PMID: 28091873
1045. Altiok E, Tiemann S, Becker M, Koos R, Zwicker C, Schroeder J, et al. Myocardial deformation imaging by two-dimensional speckle-tracking echocardiography for prediction of global and segmental functional changes after acute myocardial infarction: A comparison with late gadolinium enhancement cardiac magnetic resonance. *J Am Soc Echocardiogr* 2014; **27:** 249–257. PMID: 24368027
1046. Isaaz K, Ethevenot G, Admant P, Brembilla B, Pernot C. A new Doppler method of assessing left ventricular ejection force in chronic congestive heart failure. *Am J Cardiol* 1989; **64:** 81–87. PMID: 2741817
1047. Ciampi Q, Pratali L, Porta MD, Petruzziello B, Manganiello V, Villari B, et al. Tissue Doppler systolic velocity change during dobutamine stress echocardiography predicts contractile reserve and exercise tolerance in patients with heart failure. *Eur Heart J Cardiovasc Imaging* 2013; **14:** 102–109. PMID: 22613501
1048. Zoghbi WA. Evaluation of myocardial viability with contrast echocardiography. *Am J Cardiol* 2002; **90**(Suppl)**:** 65J–71J. PMID: 12450593
1049. Ito H, Tomooka T, Sakai N, Higashino Y, Fujii K, Katoh O, et al. Time course of functional improvement in stunned myocardium in risk area in patients with reperfused anterior infarction. *Circulation* 1993; **87:** 355–362. PMID: 8425284
1050. Pohost GM, Zir LM, Moore RH, McKusick KA, Guiney TE, Beller GA. Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 1977; **55:** 294–302. PMID: 832345
1051. Tamaki N, Yonekura Y, Yamashita K, Senda M, Saji H, Hashimoto T, et al. Relation of left ventricular perfusion and wall motion with metabolic activity in persistent defects on thallium-201 tomography in healed myocardial infarction. *Am J Cardiol* 1988; **62:** 202–208. PMID: 3261123
1052. Mori T, Minamiji K, Kurogane H, Ogawa K, Yoshida Y. Rest-injected thallium-201 imaging for assessing viability of severe asynergic regions. *J Nucl Med* 1991; **32:** 1718–1724. PMID: 1880573
1053. Ohtani H, Tamaki N, Yonekura Y, Mohiuddin IH, Hirata K, Ban T, et al. Value of thallium-201 reinjection after delayed SPECT imaging for predicting reversible ischemia after coronary artery bypass grafting. *Am J Cardiol* 1990; **66:** 394–399. PMID: 2386113
1054. Gaemperli O, Schepis T, Kalff V, Namdar M, Valenta I, Stefani L, et al. Validation of a new cardiac image fusion software for three-dimensional integration of myocardial perfusion SPECT and stand-alone 64-slice CT angiography. *Eur J Nucl Med Mol Imaging* 2007; **34:** 1097–1106. PMID: 17245532
1055. Dilsizian V, Arrighi JA, Diodati JG, Quyyumi AA, Alavi K, Bacharach SL, et al. Myocardial viability in patients with chronic coronary artery disease: Comparison of $^{99m}$Tc-sestamibi with thallium reinjection and [$^{18}$F]fluorodeoxyglucose. *Circulation* 1994; **89:** 578–587. Erratum in: *Circulation* 1995; **91:** 3026. PMID: 8313546
1056. Nishimura T, Nobuyoshi M. Clinical application of 99mTc-tetrofosmin myocardial SPECT: A multicenter trial. *Kaku Igaku* 1995; **32:** 1007–1021 (in Japanese). PMID: 8523837
1057. Kuwabara Y, Watanabe S, Nakaya J, Fujiwara M, Hasegawa R, Matsuno K, et al. Functional evaluation of myocardial viability by $^{99m}$Tc tetrofosmin gated SPECT: A quantitative comparison with $^{18}$F fluorodeoxyglucose positron emission CT ($^{18}$F FDG PET). *Ann Nucl Med* 1999; **13:** 135–140. PMID: 10435372
1058. Stollfuss JC, Haas F, Matsunari I, Neverve J, Nekolla S, Ziegler S, et al. $^{99m}$Tc-tetrofosmin SPECT for prediction of functional recovery defined by MRI in patients with severe left ventricular dysfunction: Additional value of gated SPECT. *J Nucl Med* 1999; **40:** 1824–1831. PMID: 10565777
1059. Mabuchi M, Kubo N, Morita K, Makino Y, Matsui Y, Murashita T, et al. Prediction of functional recovery after coronary bypass surgery using quantitative gated myocardial perfusion SPECT. *Nucl Med Commun* 2003; **24:** 625–631. PMID: 12766597
1060. Murashita T, Makino Y, Kamikubo Y, Yasuda K, Mabuchi M, Tamaki N. Quantitative gated myocardial perfusion single photon emission computed tomography improves the prediction of regional functional recovery in akinetic areas after coronary bypass surgery: Useful tool for evaluation of myocardial viability. *J Thorac Cardiovasc Surg* 2003; **126:** 1328–1334. PMID: 14666003
1061. Kumita S, Cho K, Nakajo H, Toba M, Kijima T, Mizumura S, Oshina T, et al. Serial assessment of left ventricular function during dobutamine stress by means of electrocardiography-gated myocardial SPECT: Combination with dual-isotope myocardial perfusion SPECT for detection of ischemic heart disease. *J Nucl Cardiol* 2001; **8:** 152–157. PMID: 11295692
1062. Leoncini M, Sciagrà R, Maioli M, Bellandi F, Marcucci G, Sestini S, et al. Usefulness of dobutamine Tc-99m sestamibi-gated single-photon emission computed tomography for prediction of left ventricular ejection fraction outcome after coronary revascularization for ischemic cardiomyopathy. *Am J Cardiol* 2002; **89:** 817–821. PMID: 11909565
1063. Yoshinaga K, Katoh C, Noriyasu K, Yamada S, Ito Y, Kuge Y, et al. Low-dose dobutamine stress gated SPET for identification of viable myocardium: Comparison with stress-rest perfusion SPET and PET. *Eur J Nucl Med Mol Imaging* 2002; **29:** 882–890. PMID: 12111128
1064. Piwnica-Worms D, Kronauge JF, Chiu ML. Uptake and retention of hexakis (2-methoxyisobutyl isonitrile) technetium(I) in cultured chick myocardial cells: Mitochondrial and plasma membrane potential dependence. *Circulation* 1990; **82:** 1826–1838. PMID: 2225379
1065. Du B, Li N, Li X, Li Y, Hsu B. Myocardial washout rate of resting $^{99m}$Tc-Sestamibi (MIBI) uptake to differentiate between normal perfusion and severe three-vessel coronary artery disease documented with invasive coronary angiography. *Ann Nucl Med* 2014; **28:** 285–292. PMID: 24395203
1066. Tsai JP, Yun CH, Wu TH, Yen CH, Hou CJ, Kuo JY, et al. A meta-analysis comparing SPECT with PET for the assessment of myocardial viability in patients with coronary artery disease. *Nucl Med Commun* 2014; **35:** 947–954. PMID: 24785009
1067. Beanlands RS, Ruddy TD, deKemp RA, Iwanochko RM,

Coates G, Freeman M, et al; PARR Investigators. Positron emission tomography and recovery following revascularization (PARR-1): The importance of scar and the development of a prediction rule for the degree of recovery of left ventricular function. *J Am Coll Cardiol* 2002; **40:** 1735–1743. PMID: 12446055
1068. Schelbert HR, Beanlands R, Bengel F, Knuuti J, Dicarli M, Machac J, et al. PET myocardial perfusion and glucose metabolism imaging. Part 2: Guidelines for interpretation and reporting. *J Nucl Cardiol* 2003; **10:** 557–571. PMID: 14569249
1069. Yoshinaga K, Katoh C, Beanlands RS, Noriyasu K, Komuro K, Yamada S, et al. Reduced oxidative metabolic response in dysfunctional myocardium with preserved glucose metabolism but with impaired contractile reserve. *J Nucl Med* 2004; **45:** 1885–1891. PMID: 15534059
1070. Sandler MP, Videlefsky S, Delbeke D, Patton JA, Meyerowitz C, Martin WH, et al. Evaluation of myocardial ischemia using a rest metabolism/stress perfusion protocol with fluorine-18 deoxyglucose/technetium-99m MIBI and dual-isotope simultaneous-acquisition single-photon emission computed tomography. *J Am Coll Cardiol* 1995; **26:** 870–878. PMID: 7560611
1071. Fujibayashi Y, Nohara R, Hosokawa R, Okuda K, Yonekura Y, Tamaki N, et al. Metabolism and kinetics of iodine-123-BMIPP in canine myocardium. *J Nucl Med* 1996; **37:** 757–761. PMID: 8965141
1072. Tamaki N, Tadamura E, Kawamoto M, Magata Y, Yonekura Y, Fujibayashi Y, et al. Decreased uptake of iodinated branched fatty acid analog indicates metabolic alterations in ischemic myocardium. *J Nucl Med* 1995; **36:** 1974–1980. PMID: 7472584
1073. Taki J, Ichikawa A, Nakajima K, Kawasuji M, Tonami N. Comparison of flow capacities of arterial and venous grafts for coronary artery bypass grafting: Evaluation with exercise thallium-201 single-photon emission tomography. *Eur J Nucl Med* 1997; **24:** 1487–1493. PMID: 9391183
1074. Franken PR, Dendale P, De Geeter F, Demoor D, Bossuyt A, Block P. Prediction of functional outcome after myocardial infarction using BMIPP and sestamibi scintigraphy. *J Nucl Med* 1996; **37:** 718–722. PMID: 8965133
1075. Blaire T, Bailliez A, Ben Bouallegue F, Bellevre D, Agostini D, Manrique A. Determination of the heart-to-mediastinum ratio of $^{123}$I-MIBG uptake using dual-isotope ($^{123}$I-MIBG/$^{99m}$Tc-Tetrofosmin) multipinhole cadmium-zinc-telluride SPECT in patients with heart failure. *J Nucl Med* 2018; **59:** 251–258. PMID: 28646015
1076. Baer FM, Voth E, LaRosée K, Schneider CA, Theissen P, Deutsch HJ, et al. Comparison of dobutamine transesophageal echocardiography and dobutamine magnetic resonance imaging for detection of residual myocardial viability. *Am J Cardiol* 1996; **78:** 415–419. PMID: 8752185
1077. Bree D, Wollmuth JR, Cupps BP, Krock MD, Howells A, Rogers J, et al. Low-dose dobutamine tissue-tagged magnetic resonance imaging with 3-dimensional strain analysis allows assessment of myocardial viability in patients with ischemic cardiomyopathy. *Circulation* 2006; **114**(Suppl)**:** I33–I36. PMID: 16820595
1078. Geskin G, Kramer CM, Rogers WJ, Theobald TM, Pakstis D, Hu YL, et al. Quantitative assessment of myocardial viability after infarction by dobutamine magnetic resonance tagging. *Circulation* 1998; **98:** 217–223. PMID: 9697821
1079. Baer FM, Theissen P, Schneider CA, Voth E, Sechtem U, Schicha H, et al. Dobutamine magnetic resonance imaging predicts contractile recovery of chronically dysfunctional myocardium after successful revascularization. *J Am Coll Cardiol* 1998; **31:** 1040–1048. PMID: 9562005
1080. Baer FM, Voth E, Schneider CA, Theissen P, Schicha H, Sechtem U. Comparison of low-dose dobutamine-gradient-echo magnetic resonance imaging and positron emission tomography with [$^{18}$F]fluorodeoxyglucose in patients with chronic coronary artery disease: A functional and morphological approach to the detection of residual myocardial viability. *Circulation* 1995; **91:** 1006–1015. PMID: 7850935
1081. Kim RJ, Hillenbrand HB, Judd RM. Evaluation of myocardial viability by MRI. *Herz* 2000; **25:** 417–430. PMID: 10948778
1082. Beanlands RS, Chow BJ, Dick A, Friedrich MG, Gulenchyn KY, Kiess M, et al. CCS/CAR/CANM/CNCS/CanSCMR joint position statement on advanced noninvasive cardiac imaging using positron emission tomography, magnetic resonance imaging and multidetector computed tomographic angiography in the diagnosis and evaluation of ischemic heart disease: Executive summary. *Can J Cardiol* 2007; **23:** 107–119. PMID: 17311116
1083. Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: An imaging study. *Lancet* 2003; **361:** 374–379. PMID: 12573373
1084. Tsao J, Boesiger P, Pruessmann KP. *k-t* BLAST and *k-t* SENSE: Dynamic MRI with high frame rate exploiting spatiotemporal correlations. *Magn Reson Med* 2003; **50:** 1031–1042. PMID: 14587014
1085. Wellnhofer E, Olariu A, Klein C, Gräfe M, Wahl A, Fleck E C, et al. Magnetic resonance low-dose dobutamine test is superior to SCAR quantification for the prediction of functional recovery. *Circulation* 2004; **109:** 2172–2174. PMID: 15117834
1086. Isbell DC, Kramer CM. Magnetic resonance for the assessment of myocardial viability. *Curr Opin Cardiol* 2006; **21:** 469–472. PMID: 16900010
1087. Motoyasu M, Sakuma H, Ichikawa Y, Ishida N, Uemura S, Okinaka T, et al. Prediction of regional functional recovery after acute myocardial infarction with low dose dobutamine stress cine MR imaging and contrast enhanced MR imaging. *J Cardiovasc Magn Reson* 2003; **5:** 563–574. PMID: 14664134
1088. Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, et al. Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: A randomised controlled trial: The CECaT trial. *Health Technol Assess* 2007; **11:** Iii–iv, ix-115. PMID: 18021576
1089. Klein C, Nekolla SG, Bengel FM, Momose M, Sammer A, Haas F, et al. Assessment of myocardial viability with contrast-enhanced magnetic resonance imaging: Comparison with positron emission tomography. *Circulation* 2002; **105:** 162–167. PMID: 11790695
1090. Selvanayagam JB, Kardos A, Francis JM, Wiesmann F, Petersen SE, Taggart DP, et al. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation* 2004; **110:** 1535–1541. PMID: 15353496
1091. Goto Y, Sakuma H. Diagnosis of cardiomyopathy using cardiovascular magnetic resonance imaging. *Nihon Naika Gakkai Zasshi* 2016; **105:** 2041–2047 (in Japanese).
1092. Schelbert EB, Messroghli DR. State of the Art: Clinical applications of cardiac T1 mapping. *Radiology* 2016; **278:** 658–676. PMID: 26885733
1093. Kali A, Choi EY, Sharif B, Kim YJ, Bi X, Spottiswoode B, et al. Native $T_1$ mapping by 3-T CMR imaging for characterization of chronic myocardial infarctions. *JACC Cardiovasc Imaging* 2015; **8:** 1019–1030. PMID: 26298071
1094. Lee HJ, Im DJ, Youn JC, Chang S, Suh YJ, Hong YJ, et al. Myocardial extracellular volume fraction with dual-energy equilibrium contrast-enhanced cardiac CT in nonischemic cardiomyopathy: A prospective comparison with cardiac MR imaging. *Radiology* 2016; **280:** 49–57. PMID: 27322972
1095. Machida H, Tanaka I, Fukui R, Shen Y, Ishikawa T, Tate E, et al. Dual-energy spectral CT: Various clinical vascular applications. *Radiographics* 2016; **36:** 1215–1232. PMID: 27399244
1096. Takaoka H, Funabashi N, Ozawa K, Uehara M, Sano K, Komuro I, et al. Improved diagnosis of detection of late enhancement in left ventricular myocardium using 2nd generation 320-slice CT reconstructed with FIRST in non-ischemic cardiomyopathy. *Int Heart J* 2018; **59:** 542–549. PMID: 29681572
1097. Sharma A, Einstein AJ, Vallakati A, Arbab-Zadeh A, Mukherjee D, Lichstein E, et al. Meta-analysis of global left ventricular function comparing multidetector computed tomography with cardiac magnetic resonance imaging. *Am J Cardiol* 2014; **113:** 731–738. PMID: 24355312
1098. Techasith T, Cury RC. Stress myocardial CT perfusion: An update and future perspective. *JACC Cardiovasc Imaging* 2011; **4:** 905–916. PMID: 21835384
1099. Sheehan FH, Mathey DG, Schofer J, Dodge HT, Bolson EL. Factors that determine recovery of left ventricular function after thrombolysis in patients with acute myocardial infarction. *Circulation* 1985; **71:** 1121–1128. PMID: 3995707
1100. Popio KA, Gorlin R, Bechtel D, Levine JA. Postextrasystolic potentiation as a predictor of potential myocardial viability: Preoperative analyses compared with studies after coronary bypass surgery. *Am J Cardiol* 1977; **39:** 944–953. PMID: 301350
1101. Matoba S, Miyao K, Tamagaki S, Katamura M, Matsumuro

A, Tsuji H, et al. Comparison of exercise-stress single photon emission computed tomography with thallium-201 reinjection and postextrasystolic potentiation to assess myocardial viability in patients with myocardial infarction. *J Cardiol* 1995; **26:** 331–339. PMID: 8558411 (in Japanese)
1102. Cooper MW. Postextrasystolic potentiation: Do we really know what it means and how to use it? *Circulation* 1993; **88:** 2962–2971. PMID: 7504591
1103. Helfant RH, Pine R, Meister SG, Feldman MS, Trout RG, Banka VS. Nitroglycerin to unmask reversible asynergy: Correlation with post coronary bypass ventriculography. *Circulation* 1974; **50:** 108–113. PMID: 4209691
1104. Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. *Circulation* 1997; **96:** 793–800. PMID: 9264484
1105. Lee KS, Marwick TH, Cook SA, Go RT, Fix JS, James KB, et al. Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction: Relative efficacy of medical therapy and revascularization. *Circulation* 1994; **90:** 2687–2694. PMID: 7994809
1106. Adachih Y, Wada H, Momomura S. Ischemic cardiomyopathy and ischemic heart failure: Ischemic heart disease. *In*: Komuro I, Nakamura M, editors. The bible for the specialist of cardiovascular medicine. Tokyo: Nakayama Shoten, 2018; 213–221 (in Japanese).
1107. Nishimura S. Diagnosis and risk stratification of ischemic heart disease. *In*: Nishimura T, editor. Brand new nuclear cardiology. Tokyo: Kanehara Shuppan, 2012: 185–196 (in Japanese).
1108. Erthal F, Chow B, Heller GV, Beanlands RSB. Nuclear cardiology procedures in the evaluation of myocardial viability. *In*: Heller GV, Hendel RC, editors. Nuclear cardiology practical applications, 3rd edn. New York: McGraw-Hill Education, 2018; 309–330.
1109. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128:** e240–e327. PMID: 23741058
1110. Rizzello V, Poldermans D, Biagini E, Schinkel AF, Boersma E, Boccanelli A, et al. Prognosis of patients with ischaemic cardiomyopathy after coronary revascularisation: Relation to viability and improvement in left ventricular ejection fraction. *Heart* 2009; **95:** 1273–1277. PMID: 19443475
1111. Senior R, Kaul S, Lahiri A. Myocardial viability on echocardiography predicts long-term survival after revascularization in patients with ischemic congestive heart failure. *J Am Coll Cardiol* 1999; **33:** 1848–1854. PMID: 10362184
1112. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016; **37:** 2315–2381. PMID: 27222591
1113. Arnold JM, Liu P, Demers C, Dorian P, Giannetti N, Haddad H, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: Diagnosis and management. *Can J Cardiol* 2006; **22:** 23–45. PMID: 16450016
1114. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation* 2003; **108:** 1404–1418. PMID: 12975245
1115. Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, et al. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *Circulation* 2009; **119:** e561–e587. PMID: 19451357
1116. Kirkpatrick JN, Vannan MA, Narula J, Lang RM, et al. Echocardiography in heart failure: Applications, utility, and new horizons. *J Am Coll Cardiol* 2007; **50:** 381–396. PMID: 17662389
1117. Nagueh SF, Bhatt R, Vivo RP, Krim SR, Sarvari SI, Russell K, et al . Echocardiographic evaluation of hemodynamics in patients with decompensated systolic heart failure. *Circ Cardiovasc Imaging* 2011; **4:** 220–227. PMID: 21398512
1118. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; **16:** 233–270. Erratum in: *Eur Heart J Cardiovasc Imaging* 2016; **17:** 412, *Eur Heart J Cardiovasc Imaging* 2016; **17:** 969. PMID: 25712077
1119. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC): Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37:** 2129–2200. Erratum in: *Eur Heart J* 2016 Dec 30. PMID: 27206819
1120. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976; **37:** 7–11. PMID: 1244736
1121. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *J Am Soc Echocardiogr* 2012; **25:** 3–46. PMID: 22183020
1122. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: Consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *J Am Soc Echocardiogr* 2015; **28:** 183–193. PMID: 25623220
1123. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: Evolving knowledge. *J Am Coll Cardiol* 2009; **54:** 1561–1575. PMID: 19833255
1124. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; **23:** 685–713. PMID: 20620859
1125. Al Jaroudi W, Iskandrian AE. Regadenoson: A new myocardial stress agent. *J Am Coll Cardiol* 2009; **54:** 1123–1130. PMID: 19761931
1126. Hendel RC, Patel MR, Kramer CM, Poon M, Hendel RC, Carr JC, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: A report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006; **48:** 1475–1497. PMID: 17010819
1127. Gonzalez JA, Kramer CM. Role of imaging techniques for diagnosis, prognosis and management of heart failure patients: Cardiac magnetic resonance. *Curr Heart Fail Rep* 2015; **12:** 276–283. PMID: 26041670
1128. Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation* 2010; **121:** 2462–2508. PMID: 20479157
1129. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. *J Am Coll Cardiol* 2009; **54:** 1407–1424.

PMID: 19796734
1130. Moon JC, Messroghli DR, Kellman P, Piechnik SK, Robson MD, Ugander M, et al. Myocardial T1 mapping and extracellular volume quantification: A Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson* 2013; **15:** 92. PMID: 24124732
1131. Rizvi A, Deaño RC, Bachman DP, Xiong G, Min JK, Truong QA, et al. Analysis of ventricular function by CT. *J Cardiovasc Comput Tomogr* 2015; **9:** 1–12. PMID: 25576407
1132. Wai B, Thai WE, Brown H, Truong QA. Novel phase-based noise reduction strategy for quantification of left ventricular function and mass assessment by cardiac CT: Comparison with cardiac magnetic resonance. *Eur J Radiol* 2013; **82:** e337–e341. PMID: 23522745
1133. Asferg C, Usinger L, Kristensen TS, Abdulla J. Accuracy of multi-slice computed tomography for measurement of left ventricular ejection fraction compared with cardiac magnetic resonance imaging and two-dimensional transthoracic echocardiography: A systematic review and meta-analysis. *Eur J Radiol* 2012; **81:** e757–e762. PMID: 22381439
1134. Mahabadi AA, Samy B, Seneviratne SK, Toepker MH, Bamberg F, Hoffmann U, et al. Quantitative assessment of left atrial volume by electrocardiographic-gated contrast-enhanced multidetector computed tomography. *J Cardiovasc Comput Tomogr* 2009; **3:** 80–87. PMID: 19332340
1135. Stojanovska J, Prasitdumrong H, Patel S, Sundaram B, Gross BH, Yilmaz ZN, et al. Reference absolute and indexed values for left and right ventricular volume, function and mass from cardiac computed tomography. *J Med Imaging Radiat Oncol* 2014; **58:** 547–558. PMID: 24821646
1136. Dodge HT, Sandler H, Ballew DW, Lord JD Jr. The use of biplane angiocardigraphy for the measurement of left ventricular volume in man. *Am Heart J* 1960; **60:** 762–776. PMID: 13723340
1137. Chapman CB, Baker O, Reynolds J, Bonte FJ. Use of biplane cinefluorography for measurement of ventricular volume. *Circulation* 1958; **18:** 1105–1117. PMID: 13608839
1138. Sheehan FH, Bolson EL, Dodge HT, Mathey DG, Schofer J, Woo HW. Advantages and applications of the centerline method for characterizing regional ventricular function. *Circulation* 1986; **74:** 293–305. PMID: 3731420
1139. Sheehan FH, Schofer J, Mathey DG, Kellett MA, Smith H, Bolson EL, et al. Measurement of regional wall motion from biplane contrast ventriculograms: A comparison of the 30 degree right anterior oblique and 60 degree left anterior oblique projections in patients with acute myocardial infarction. *Circulation* 1986; **74:** 796–804. PMID: 3757191
1140. Peterson KL, Skloven D, Ludbrook P, Uther JB, Ross J Jr. Comparison of isovolumic and ejection phase indices of myocardial performance in man. *Circulation* 1974; **49:** 1088–1101. PMID: 4831653
1141. Dewey M, Müller M, Eddicks S, Schnapauff D, Teige F, Rutsch W, et al. Evaluation of global and regional left ventricular function with 16-slice computed tomography, biplane cineventriculography, and two-dimensional transthoracic echocardiography: Comparison with magnetic resonance imaging. *J Am Coll Cardiol* 2006; **48:** 2034–2044. PMID: 17112993
1142. McKay RG, Spears JR, Aroesty JM, Baim DS, Royal HD, Heller GV, et al. Instantaneous measurement of left and right ventricular stroke volume and pressure-volume relationships with an impedance catheter. *Circulation* 1984; **69:** 703–710. PMID: 6697458
1143. Kass DA, Midei M, Graves W, Brinker JA, Maughan WL. Use of a conductance (volume) catheter and transient inferior vena caval occlusion for rapid determination of pressure-volume relationships in man. *Cathet Cardiovasc Diagn* 1988; **15:** 192–202. PMID: 3197110
1144. Fujita M, Sasayama S, Kawai C, Eiho S, Kuwahara M. Automatic processing of cineventriculograms for analysis of regional myocardial function. *Circulation* 1981; **63:** 1065–1074. PMID: 7471366
1145. Hirota Y. A clinical study of left ventricular relaxation. *Circulation* 1980; **62:** 756–763. PMID: 7190882
1146. Thompson DS, Waldron CB, Juul SM, Naqvi N, Swanton RH, Coltart DJ, et al. Analysis of left ventricular pressure during isovolumic relaxation in coronary artery disease. *Circulation* 1982; **65:** 690–697. PMID: 7060246
1147. Nonogi H, Hess OM, Bortone AS, Ritter M, Carroll JD, Krayenbuehl HP. Left ventricular pressure-length relation during exercise-induced ischemia. *J Am Coll Cardiol* 1989; **13:** 1062–1070. PMID: 2926056
1148. Taegtmeyer H. Metabolic crosstalk in heart failure: New roles for B-type natriuretic peptide. *J Am Coll Cardiol* 2011; **58:** 1126–1127. PMID: 21884949
1149. Mock MB, Ringqvist I, Fisher LD, Davis KB, Chaitman BR, Kouchoukos NT, et al. Survival of medically treated patients in the coronary artery surgery study (CASS) registry. *Circulation* 1982; **66:** 562–568. PMID: 6980062
1150. Nagao T, Chikamori T, Hida S, Igarashi Y, Kuwabara Y, Nishimura S, et al; Q-PROVE Study Group. Quantitative gated single-photon emission computed tomography with $^{99m}$Tc sestamibi predicts major cardiac events in elderly patients with known or suspected coronary artery disease: The QGS-Prognostic Value in the Elderly (Q-PROVE) Study. *Circ J* 2007; **71:** 1029–1034. PMID: 17587706
1151. Schepis T, Benz K, Haldemann A, Kaufmann PA, Schmidhauser C, Frielingsdorf J, et al. Prognostic value of stress-gated 99 m-technetium SPECT myocardial perfusion imaging: Risk stratification of patients with multivessel coronary artery disease and prior coronary revascularization. *J Nucl Cardiol* 2013; **20:** 755–762. PMID: 23839243
1152. Motwani M, Swoboda PP, Plein S, Greenwood JP. Role of cardiovascular magnetic resonance in the management of patients with stable coronary artery disease. *Heart* 2018; **104:** 888–894. PMID: 29170357
1153. Salerno M, Sharif B, Arheden H, Kumar A, Axel L, Li D, et al. Recent advances in cardiovascular magnetic resonance: Techniques and applications. *Circ Cardiovasc Imaging* 2017; **10:** E003951. PMID: 28611116
1154. Patel MR, Bailey SR, Bonow RO, Chambers CE, Chan PS, Dehmer GJ, et al. ACCF/SCAI/AATS/AHA/ASE/ASNC/HFSA/HRS/SCCM/SCCT/SCMR/STS 2012 appropriate use criteria for diagnostic catheterization: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012; **59:** 1995–2027. PMID: 22578925
1155. Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, et al. Impact of the pulmonary artery catheter in critically ill patients: Meta-analysis of randomized clinical trials. *JAMA* 2005; **294:** 1664–1670. PMID: 16204666
1156. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, et al; Japanese Circulation Society and the Japanese Heart Failure Society Joint Working Group. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure: Digest version. *Circ J* 2019; **83:** 2084–2184. PMID: 31511439
1157. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, et al; ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: The ESCAPE trial. *JAMA* 2005; **294:** 1625–1633. PMID: 16204662
1158. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; **128:** 1810–1852. PMID: 23741057
1159. Leischik R, Dworrak B, Littwitz H, Gülker H. Prognostic significance of exercise stress echocardiography in 3329 outpatients (5-year longitudinal study). *Int J Cardiol* 2007; **119:** 297–305. PMID: 17113169
1160. Shah BN, Balaji G, Alhajiri A, Ramzy IS, Ahmadvazir S, Senior R. Incremental diagnostic and prognostic value of contemporary stress echocardiography in a chest pain unit: Mortality and morbidity outcomes from a real-world setting. *Circ Cardiovasc Imaging* 2013; **6:** 202–209. PMID: 23258477
1161. Bajaj NS, Singh S, Farag A, El-Hajj S, Heo J, Iskandrian AE, et al. The prognostic value of non-perfusion variables obtained during vasodilator stress myocardial perfusion imaging. *J Nucl Cardiol* 2016; **23:** 390–413. PMID: 26940574
1162. Shaw LJ, Cerqueira MD, Brooks MM, Althouse AD, Sansing VV, Beller GA, et al. Impact of left ventricular function and the extent of ischemia and scar by stress myocardial perfusion

imaging on prognosis and therapeutic risk reduction in diabetic patients with coronary artery disease: Results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *J Nucl Cardiol* 2012; **19:** 658–669. PMID: 22527794
1163. McCully RB, Roger VL, Mahoney DW, Burger KN, Click RL, Seward JB, et al. Outcome after abnormal exercise echocardiography for patients with good exercise capacity: Prognostic importance of the extent and severity of exercise-related left ventricular dysfunction. *J Am Coll Cardiol* 2002; **39:** 1345–1352. PMID: 11955853
1164. Mordi I, Tzemos N. Non-invasive assessment of coronary artery disease in patients with left bundle branch block. *Int J Cardiol* 2015; **184:** 47–55. PMID: 25697870
1165. America YG, Bax JJ, Boersma E, Stokkel M, van der Wall EE. Prognostic value of gated SPECT in patients with left bundle branch block. *J Nucl Cardiol* 2007; **14:** 75–81. PMID: 17276309
1166. Wong ND, Cupples LA, Ostfeld AM, Levy D, Kannel WB. Risk factors for long-term coronary prognosis after initial myocardial infarction: The Framingham Study. *Am J Epidemiol* 1989; **130:** 469–480. PMID: 2763992
1167. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007; **297:** 1197–1206. PMID: 17374814
1168. Wong ND, Wilson PW, Kannel WB. Serum cholesterol as a prognostic factor after myocardial infarction: The Framingham Study. *Ann Intern Med* 1991; **115:** 687–693. PMID: 1929036
1169. van Miltenburg-van Zijl AJ, Simoons ML, Veerhoek RJ, Bossuyt PM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. *J Am Coll Cardiol* 1995; **25:** 1286–1292. PMID: 7722122
1170. Abidov A, Rozanski A, Hachamovitch R, Hayes SW, Aboul-Enein F, Cohen I, et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. *N Engl J Med* 2005; **353:** 1889–1898. PMID: 16267320
1171. Marschner IC, Colquhoun D, Simes RJ, Glasziou P, Harris P, Singh BB, et al; LIPID Study Investigators. Long-term risk stratification for survivors of acute coronary syndromes: Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. *J Am Coll Cardiol* 2001; **38:** 56–63. PMID: 11451296
1172. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. Guidelines on the management of stable angina pectoris: Executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006; **27:** 1341–1381. PMID: 16735367
1173. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; **107:** 499–511. PMID: 12551878
1174. Ridker PM. High-sensitivity C-reactive protein, vascular imaging, and vulnerable plaque: More evidence to support trials of antiinflammatory therapy for cardiovascular risk reduction. *Circ Cardiovasc Imaging* 2011; **4:** 195–197. PMID: 21586741
1175. Kragelund C, Grønning B, Køber L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005; **352:** 666–675. PMID: 15716560
1176. Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: A community-based cohort study. *Circulation* 2006; **113:** 1071–1078. PMID: 16490824
1177. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, et al. Assessment of functional capacity in clinical and research settings: A Scientific Statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation* 2007; **116:** 329–343. PMID: 17576872
1178. Elhendy A, Mahoney DW, Burger KN, McCully RB, Pellikka PA. Prognostic value of exercise echocardiography in patients with classic angina pectoris. *Am J Cardiol* 2004; **94:** 559–563. PMID: 15342283
1179. Beller GA, Zaret BL. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. *Circulation* 2000; **101:** 1465–1478. PMID: 10736294
1180. Hachamovitch R, Berman DS, Kiat H, Cohen I, Lewin H, Amanullah A, et al. Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. *Am J Cardiol* 1997; **80:** 426–433. PMID: 9285653
1181. Abidov A, Bax JJ, Hayes SW, Hachamovitch R, Cohen I, Gerlach J, et al. Transient ischemic dilation ratio of the left ventricle is a significant predictor of future cardiac events in patients with otherwise normal myocardial perfusion SPECT. *J Am Coll Cardiol* 2003; **42:** 1818–1825. PMID: 14642694
1182. Steinberg EH, Koss JH, Lee M, Grunwald AM, Bodenheimer MM. Prognostic significance from 10-year follow-up of a qualitatively normal planar exercise thallium test in suspected coronary artery disease. *Am J Cardiol* 1993; **71:** 1270–1273. PMID: 8498365
1183. Joki N, Hase H, Kawano Y, Nakamura S, Nakajima K, Hatta T, et al. Myocardial perfusion imaging for predicting cardiac events in Japanese patients with advanced chronic kidney disease: 1-year interim report of the J-ACCESS 3 investigation. *Eur J Nucl Med Mol Imaging* 2014; **41:** 1701–1709. PMID: 24827603
1184. Matsuo S, Nakajima K, Yamasaki Y, Kashiwagi A, Nishimura T. Prognostic value of normal stress myocardial perfusion imaging and ventricular function in Japanese asymptomatic patients with type 2 diabetes: A study based on the J-ACCESS-2 database. *Circ J* 2010; **74:** 1916–1921. PMID: 20631452
1185. Imamura Y, Fukuyama T, Nishimura S, Nishimura T. Japanese Assessment of Cardiac Events and Survival Study (J-ACCESS): Normal myocardial perfusion scan portends a benign prognosis independent from the pretest probability of coronary artery disease. Sub-analysis of the J-ACCESS study. *J Cardiol* 2009; **54:** 93–100. PMID: 19632527
1186. Nakajima K, Nishimura T. Prognostic table for predicting major cardiac events based on J-ACCESS investigation. *Ann Nucl Med* 2008; **22:** 891–897. PMID: 19142708
1187. Nakata T, Hashimoto A, Wakabayashi T, Kusuoka H, Nishimura T. Prediction of new-onset refractory congestive heart failure using gated myocardial perfusion SPECT imaging in patients with known or suspected coronary artery disease: Subanalysis of the J-ACCESS database. *JACC Cardiovasc Imaging* 2009; **2:** 1393–1400. PMID: 20083074
1188. Yoda S, Hori Y, Hayase M, Mineki T, Hatta T, Suzuki Y, et al. Correlation between early revascularization and major cardiac events demonstrated by ischemic myocardium in Japanese patients with stable coronary artery disease. *J Cardiol* 2018; **71:** 44–51. PMID: 28732592
1189. Nakajima K, Kusuoka H, Nishimura S, Yamashina A, Nishimura T. Prognostic value of myocardial perfusion and ventricular function in a Japanese multicenter cohort study (J-ACCESS): The first-year total events and hard events. *Ann Nucl Med* 2009; **23:** 373–381. PMID: 19363705
1190. Nakajima K, Nakamura S, Hase H, Takeishi Y, Nishimura S, Kawano Y, et al. Risk stratification based on J-ACCESS risk models with myocardial perfusion imaging: Risk versus outcomes of patients with chronic kidney disease. *J Nucl Cardiol* 2020; **27:** 41–50. PMID: 29948890
1191. Nishimura M, Hashimoto T, Tamaki N, Kobayashi H, Ono T. Focal impairment in myocardial fatty acid imaging in the left anterior descending artery area, a strong predictor for cardiac death in hemodialysis patients without obstructive coronary artery disease. *Eur J Nucl Med Mol Imaging* 2015; **42:** 1612–1621. PMID: 26112389
1192. Hashimoto H, Nakanishi R, Mizumura S, Hashimoto Y, Okamura Y, Kiuchi S, et al. Prognostic value of $^{123}$I-BMIPP SPECT in patients with nonischemic heart failure with preserved ejection fraction. *J Nucl Med* 2018; **59:** 259–265. PMID: 28775200
1193. Johnson NP, Gould KL, Di Carli MF, Taqueti VR. Invasive FFR and noninvasive CFR in the evaluation of ischemia: What is the future? *J Am Coll Cardiol* 2016; **67:** 2772–2788. PMID: 27282899
1194. Naya M, Murthy VL, Foster CR, Gaber M, Klein J, Hainer J, et al. Prognostic interplay of coronary artery calcification and underlying vascular dysfunction in patients with suspected coronary artery disease. *J Am Coll Cardiol* 2013; **61:** 2098–2106. PMID: 23524053
1195. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol* 2018; **72:** 434–447. PMID: 30025580
1196. Blaha MJ, Budoff MJ, DeFilippis AP, Blankstein R, Rivera JJ,

Agatston A, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: Implications for the JUPITER population from MESA, a population-based cohort study. *Lancet* 2011; **378:** 684–692. PMID: 21856482
1197. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, et al. Diagnostic and prognostic value of absence of coronary artery calcification. *JACC Cardiovasc Imaging* 2009; **2:** 675–688. PMID: 19520336
1198. Schulman-Marcus J, Lin FY, Gransar H, Berman D, Callister T, DeLago A, et al. Coronary revascularization vs. medical therapy following coronary-computed tomographic angiography in patients with low-, intermediate- and high-risk coronary artery disease: Results from the CONFIRM long-term registry. *Eur Heart J Cardiovasc Imaging* 2017; **18:** 841–848. PMID: 28329294
1199. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol* 2015; **66:** 337–346. PMID: 26205589
1200. Otake H, Taylor CA, Matsuo H, Tanaka N, Akasaka T. Non-invasive fractional flow reserve derived from coronary computed tomography angiography: Is this just another new diagnostic test or the long-awaited game changer? *Circ J* 2017; **81:** 1085–1093. PMID: 28413187
1201. Nadjiri J, Hausleiter J, Jähnichen C, Will A, Hendrich E, Martinoff S, et al. Incremental prognostic value of quantitative plaque assessment in coronary CT angiography during 5 years of follow up. *J Cardiovasc Comput Tomogr* 2016; **10:** 97–104. PMID: 26837235
1202. Blanke P, Naoum C, Ahmadi A, Cheruvu C, Soon J, Arepalli C, et al. Long-term prognostic utility of coronary CT angiography in stable patients with diabetes mellitus. *JACC Cardiovasc Imaging* 2016; **9:** 1280–1288. PMID: 27568114
1203. Feuchtner G, Kerber J, Burghard P, Dichtl W, Friedrich G, Bonaros N, et al. The high-risk criteria low-attenuation plaque <60 HU and the napkin-ring sign are the most powerful predictors of MACE: A long-term follow-up study. *Eur Heart J Cardiovasc Imaging* 2017; **18:** 772–779. PMID: 27502292
1204. Nørgaard BL, Hjort J, Gaur S, Hansson N, Bøtker HE, Leipsic J, et al. Clinical use of coronary CTA-derived FFR for decision-making in stable CAD. *JACC Cardiovasc Imaging* 2017; **10:** 541–550. PMID: 27085447
1205. Curzen NP, Nolan J, Zaman AG, Nørgaard BL, Rajani R. Does the routine availability of CT-derived FFR influence management of patients with stable chest pain compared to CT angiography alone?: The $FFR_{CT}$ RIPCORD Study. *JACC Cardiovasc Imaging* 2016; **9:** 1188–1194. PMID: 27568119
1206. Kwong RY, Sattar H, Wu H, Vorobiof G, Gandla V, Steel K, et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation* 2008; **118:** 1011–1020. PMID: 18725488
1207. Steel K, Broderick R, Gandla V, Larose E, Resnic F, Jerosch-Herold M, et al. Complementary prognostic values of stress myocardial perfusion and late gadolinium enhancement imaging by cardiac magnetic resonance in patients with known or suspected coronary artery disease. *Circulation* 2009; **120:** 1390–1400. PMID: 19770399
1208. Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR Jr, Chaitman BR, et al. Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994; **90:** 2645–2657. PMID: 7994804
1209. Califf RM, Armstrong PW, Carver JR, D'Agostino RB, Strauss WE. Task Force 5: Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol* 1996; **27:** 1007–1019. PMID: 8609316
1210. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, et al. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009; **5:** 50–56. PMID: 19577983
1211. Tanaka N, Nakamura M, Akasaka T, Kadota K, Uemura S, Amano T, et al; CVIT-DEFER Registry Investigators. One-year outcome of fractional flow reserve-based coronary intervention in Japanese daily practice: CVIT-DEFER Registry. *Circ J* 2017; **81:** 1301–1306. PMID: 28450667
1212. Yanagisawa H, Chikamori T, Tanaka N, Hatano T, Morishima T, Hida S, et al. Correlation between thallium-201 myocardial perfusion defects and the functional severity of coronary artery stenosis as assessed by pressure-derived myocardial fractional flow reserve. *Circ J* 2002; **66:** 1105–1109. PMID: 12499614
1213. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes. *JACC Cardiovasc Interv* 2016; **9:** 1022–1031. PMID: 27198682
1214. Kimura Y, Tanaka N, Okura H, Yoshida K, Akabane M, Takayama T, et al. Characterization of real-world patients with low fractional flow reserve immediately after drug-eluting stents implantation. *Cardiovasc Interv Ther* 2016; **31:** 29–37. PMID: 26135607
1215. Tanaka N, Pijls NH, Yamashita J, Kimura Y, Ogawa M, Murata N, et al. Analysis of suboptimal stent deployment using intravascular ultrasound and coronary pressure pullback measurement. *J Cardiol* 2017; **69:** 613–618. PMID: 27876181
1216. Sakoda K, Tanaka N, Hokama Y, Hoshino K, Murata N, Yamashita J, et al. Association of moderate chronic kidney disease with insufficient improvement of fractional flow reserve after stent implantation. *Catheter Cardiovasc Interv* 2016; **88:** E38–E44. PMID: 26489880
1217. Lee JM, Koo BK, Shin ES, Nam CW, Doh JH, Hwang D, et al. Clinical implications of three-vessel fractional flow reserve measurement in patients with coronary artery disease. *Eur Heart J* 2018; **39:** 945–951. PMID: 29020260
1218. Taqueti VR, Hachamovitch R, Murthy VL, Naya M, Foster CR, Hainer J, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. *Circulation* 2015; **131:** 19–27. PMID: 25400060
1219. Ahn SG, Suh J, Hung OY, Lee HS, Bouchi YH, Zeng W, et al. Discordance between fractional flow reserve and coronary flow reserve: Insights from intracoronary imaging and physiological assessment. *JACC Cardiovasc Interv* 2017; **10:** 999–1007. PMID: 28521932
1220. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; **364:** 226–235. PMID: 21247313
1221. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. *JAMA* 2008; **300:** 1765–1773. PMID: 18854538
1222. Nakata T, Nagao K, Tsuchihashi K, Hashimoto A, Tanaka S, Iimura O. Regional cardiac sympathetic nerve dysfunction and the diagnostic efficacy of metaiodobenzylguanidine tomography in stable coronary artery disease. *Am J Cardiol* 1996; **78:** 292–297. PMID: 8759807
1223. Tateno M, Tamaki N, Yukihiro M, Kudoh T, Hattori N, Tadamura E, et al. Assessment of fatty acid uptake in ischemic heart disease without myocardial infarction. *J Nucl Med* 1996; **37:** 1981–1985. PMID: 8970518
1224. Yamamoto H, Kitagawa T, Ohashi N, Utsunomiya H, Kunita E, Oka T, et al. Noncalcified atherosclerotic lesions with vulnerable characteristics detected by coronary CT angiography and future coronary events. *J Cardiovasc Comput Tomogr* 2013; **7:** 192–199. PMID: 23849492
1225. Amanuma M, Kondo T, Sano T, Sekine T, Takayanagi T, Matsutani H, et al. Subtraction coronary computed tomography in patients with severe calcification. *Int J Cardiovasc Imaging* 2015; **31:** 1635–1642. PMID: 26288954
1226. Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG, et al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: A report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation. *J Am Coll Cardiol* 2012; **59:** 1058–1072. PMID: 22421299
1227. Masumura Y, Ueda Y, Matsuo K, Akazawa Y, Nishio M, Hirata A, et al. Frequency and location of yellow and disrupted coronary plaques in patients as detected by angioscopy. *Circ J* 2011; **75:** 603–612. PMID: 21187655
1228. Miller DD, Donohue TJ, Younis LT, Bach RG, Aguirre FV, Wittry MD, et al. Correlation of pharmacological $^{99m}$Tc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. *Circulation* 1994; **89:** 2150–2160. PMID: 8181140
1229. Nakajima K, Nishimura T. Cardiovascular events in Japan: Lessons from the J-ACCESS multicenter prognostic study

using myocardial perfusion imaging. *Circ J* 2012; **76:** 1313–1321. PMID: 22572460
1230. Shiga T, Hagiwara N, Ogawa H, Takagi A, Nagashima M, Yamauchi T, et al; Heart Institute of Japan Acute Myocardial Infarction-II (HIJAMI-II) Investigators. Sudden cardiac death and left ventricular ejection fraction during long-term follow-up after acute myocardial infarction in the primary percutaneous coronary intervention era: Results from the HIJAMI-II registry. *Heart* 2009; **95:** 216–220. PMID: 18728065
1231. Gorcsan J. Echocardiographic strain imaging for myocardial viability: An improvement over visual assessment? *Circulation* 2005; **112:** 3820–3822. PMID: 16365206
1232. Ordovas KG, Higgins CB. Delayed contrast enhancement on MR images of myocardium: Past, present, future. *Radiology* 2011; **261:** 358–374. PMID: 22012903
1233. Kasama S, Toyama T, Sumino H, Kumakura H, Takayama Y, Minami K, et al. Prognostic value of cardiac sympathetic nerve activity evaluated by [$^{123}$I]m-iodobenzylguanidine imaging in patients with ST-segment elevation myocardial infarction. *Heart* 2011; **97:** 20–26. PMID: 21062772
1234. Carpeggiani C1, Emdin M, Bonaguidi F, Landi P, Michelassi C, Trivella MG, et al. Personality traits and heart rate variability predict long-term cardiac mortality after myocardial infarction. *Eur Heart J* 2005; **26:** 1612–1617. PMID: 15827060
1235. Inobe Y, Kugiyama K, Miyagi H, Ohgushi M, Tomiguchi S, Takahashi M, et al. Long-lasting abnormalities in cardiac sympathetic nervous system in patients with coronary spastic angina: Quantitative analysis with iodine 123 metaiodobenzylguanidine myocardial scintigraphy. *Am Heart J* 1997; **134:** 112–118. PMID: 9266791
1236. Zellweger MJ, Hachamovitch R, Kang X, Hayes SW, Friedman JD, Germano G, et al. Threshold, incidence, and predictors of prognostically high-risk silent ischemia in asymptomatic patients without prior diagnosis of coronary artery disease. *J Nucl Cardiol* 2009; **16:** 193–200. PMID: 19156480
1237. Piepoli MF, Davos C, Francis DP, Coats AJ, ExTraMATCH Collaborative. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004; **328:** 189. PMID: 14729656
1238. Marchionni N, Fattirolli F, Fumagalli S, Oldridge N, Del Lungo F, Morosi L, et al. Improved exercise tolerance and quality of life with cardiac rehabilitation of older patients after myocardial infarction: Results of a randomized, controlled trial. *Circulation* 2003; **107:** 2201–2206. PMID: 12707240
1239. He Z, Liu Y, Shi R, Guo X, Wang Y, Lu P, et al. Clinical evaluation of 99 mTc-MIBI myocardial tomography for detecting coronary artery disease. *Chin Med Sci J* 1992; **7:** 1–4. PMID: 1421354
1240. Bax JJ, Fath-Ordoubadi F, Boersma E, Wijns W, Camici PG. Accuracy of PET in predicting functional recovery after revascularisation in patients with chronic ischaemic dysfunction: Head-to-head comparison between blood flow, glucose utilisation and water-perfusable tissue fraction. *Eur J Nucl Med Mol Imaging* 2002; **29:** 721–727. PMID: 12029544
1241. Hoffmann U, Moselewski F, Nieman K, Jang IK, Ferencik M, Rahman AM, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. *J Am Coll Cardiol* 2006; **47:** 1655–1662. PMID: 16631006
1242. Bech GJ, De Bruyne B, Pijls NH, de Muinck ED, Hoorntje JC, Escaned J, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: A randomized trial. *Circulation* 2001; **103:** 2928–2934. PMID: 11413082
1243. Samady H, McDaniel M, Veledar E, De Bruyne B, Pijls NH, Fearon WF, et al. Baseline fractional flow reserve and stent diameter predict optimal post-stent fractional flow reserve and major adverse cardiac events after bare-metal stent deployment. *JACC Cardiovasc Interv* 2009; **2:** 357–363. PMID: 19463450
1244. Li SJ, Ge Z, Kan J, Zhang JJ, Ye F, Kwan TW, et al. Cutoff value and long-term prediction of clinical events by FFR measured immediately after implantation of a drug-eluting stent in patients with coronary artery disease: 1- to 3-year results from the DKCRUSH VII Registry Study. *JACC Cardiovasc Interv* 2017; **10:** 986–995. PMID: 28456699
1245. Toyama S, Kato K, Harumi K, Yanaga T, Murayama M, Taniguchi K, et al. The Japanese Society of Electrocardiology report from antianginal drugs expert committee. *Jpn J Electrocardiogr* 1996; **16:** 83–88 (in Japanese).
1246. Saito M, Asonuma H, Tomita M, Sumiyoshi T, Haze K, Fukami K, et al. Differentiation of myocardial ischemia and left ventricular aneurysm in the genesis of exercise-induced ST-T changes in previous anterior myocardial infarction. *Jpn Circ J* 1987; **51:** 503–510. PMID: 3626010
1247. Davis TM, Coleman RL, Holman RR. UKPDS Group. Prognostic significance of silent myocardial infarction in newly diagnosed type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 79. *Circulation* 2013; **127:** 980–987. PMID: 23362315
1248. Yamazaki J, Iida M, Igarashi M, Hosoi H, Ishiguro S, Hou M, et al. Evaluation of the efficacy of nicorandil in patients with ischemic heart disease by exercise Tl-201 myocardial SPECT. *Int J Clin Pharmacol Ther* 1994; **32:** 183–191. PMID: 8032578
1249. Tamaki S, Nakajima H, Murakami T, Yui Y, Kambara H, Kadota K, et al. Estimation of infarct size by myocardial emission computed tomography with thallium-201 and its relation to creatine kinase-MB release after myocardial infarction in man. *Circulation* 1982; **66:** 994–1001. PMID: 6982116
1250. Rossi A, Dini FL, Faggiano P, Agricola E, Cicoira M, Frattini S, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure: A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* 2011; **97:** 1675–1680. PMID: 21807656
1251. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am J Cardiol* 2003; **91:** 538–543. PMID: 12615256
1252. Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G, et al. Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *J Am Coll Cardiol* 2010; **55:** 2470–2479. PMID: 20510214
1253. Bingham SE, Hachamovitch R. Incremental prognostic significance of combined cardiac magnetic resonance imaging, adenosine stress perfusion, delayed enhancement, and left ventricular function over preimaging information for the prediction of adverse events. *Circulation* 2011; **123:** 1509–1518. PMID: 21444886
1254. Taki J, Yasuhara S, Takamatsu T, Nakajima K, Tatami R, Ishise S, et al. Value of iodine-123 metaiodobenzylguanidine scintigraphy in patients with vasospastic angina. *Eur J Nucl Med* 1998; **25:** 229–234. PMID: 9580854
1255. Sakata K, Iida K, Kudo M, Yoshida H, Doi O. Prognostic value of I-123 metaiodobenzylguanidine imaging in vasospastic angina without significant coronary stenosis. *Circ J* 2005; **69:** 171–176. PMID: 15671608
1256. Watanabe K, Takahashi T, Miyajima S, Hirokawa Y, Tanabe N, Kato K, et al. Myocardial sympathetic denervation, fatty acid metabolism, and left ventricular wall motion in vasospastic angina. *J Nucl Med* 2002; **43:** 1476–1481. PMID: 12411551
1257. Mark DB, Califf RM, Morris KG, Harrell FE Jr, Pryor DB, Hlatky MA, et al. Clinical characteristics and long-term survival of patients with variant angina. *Circulation* 1984; **69:** 880–888. PMID: 6705163
1258. Yasue H, Takizawa A, Nagao M, Nishida S, Horie M, Kubota J, et al. Long-term prognosis for patients with variant angina and influential factors. *Circulation* 1988; **78:** 1–9. PMID: 3260150
1259. Shimokawa H, Nagasawa K, Irie T, Egashira S, Egashira K, Sagara T, et al. Clinical characteristics and long-term prognosis of patients with variant angina: A comparative study between western and Japanese populations. *Int J Cardiol* 1988; **18:** 331–349. PMID: 3129375
1260. Weiner DA, Ryan TJ, McCabe CH, Luk S, Chaitman BR, Sheffield LT, et al. Significance of silent myocardial ischemia during exercise testing in patients with coronary artery disease. *Am J Cardiol* 1987; **59:** 725–729. PMID: 3825930
1261. Detry JM, Robert A, Luwaert RJ, Melin JA. Prognostic significance of silent exertional myocardial ischaemia in symptomatic men without previous myocardial infarction. *Eur Heart J* 1992; **13:** 183–187. PMID: 1555614
1262. Raiker K, Sinusas AJ, Wackers FJ, Zaret BL. One-year prognosis of patients with normal planar or single-photon emission computed tomographic technetium 99 m-labeled sestamibi exercise imaging. *J Nucl Cardiol* 1994; **1:** 449–456. PMID: 9420729
1263. Boiten HJ, van Domburg RT, Valkema R, Schinkel AF. Eleven-year prognostic value of dobutamine stress $^{99m}$Tc-sestamibi myocardial perfusion imaging in patients with limited

exercise capacity. *Am J Cardiol* 2015; **115:** 884–889. PMID: 25661571
1264. Navare SM, Katten D, Johnson LL, Mather JF, Fowler MS, Ahlberg AW, et al. Risk stratification with electrocardiographic-gated dobutamine stress technetium-99m sestamibi single-photon emission tomographic imaging: Value of heart rate response and assessment of left ventricular function. *J Am Coll Cardiol* 2006; **47:** 781–788. PMID: 16487845
1265. De Lorenzo A, Lima RS, Siqueira-Filho AG, Pantoja MR. Prevalence and prognostic value of perfusion defects detected by stress technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography in asymptomatic patients with diabetes mellitus and no known coronary artery disease. *Am J Cardiol* 2002; **90:** 827–832. PMID: 12372568
1266. McCully RB, Roger VL, Mahoney DW, Karon BL, Oh JK, Miller FA Jr, et al. Outcome after normal exercise echocardiography and predictors of subsequent cardiac events: Follow-up of 1,325 patients. *J Am Coll Cardiol* 1998; **31:** 144–149. PMID: 9426033
1267. Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K et al. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: A comparative study using intravascular ultrasound. *J Am Coll Cardiol* 2006; **47:** 672–677. PMID: 16458154
1268. Papadopoulou SL, Neefjes LA, Schaap M, Li HL, Capuano E, van der Giessen AG, et al. Detection and quantification of coronary atherosclerotic plaque by 64-slice multidetector CT: A systematic head-to-head comparison with intravascular ultrasound. *Atherosclerosis* 2011; **219:** 163–170. PMID: 21802687
1269. Lansky AJ, Brar SS, Yaqub M, Sood P, Applegate RJ, Lazar D, et al. Impact of routine angiographic follow-up after percutaneous coronary intervention with drug-eluting stents in the SPIRIT III randomized trial at three years. *Am J Cardiol* 2012; **110:** 21–29. PMID: 22464212
1270. Uchida T, Popma J, Stone GW, Ellis SG, Turco MA, Ormiston JA, et al. The clinical impact of routine angiographic follow-up in randomized trials of drug-eluting stents: A critical assessment of "oculostenotic" reintervention in patients with intermediate lesions. *JACC Cardiovasc Interv* 2010; **3:** 403–411. PMID: 20398868
1271. ten Berg JM, Kelder JC, Suttorp MJ, Verheugt FW, Thijs Plokker HW, et al. Influence of planned six-month follow-up angiography on late outcome after percutaneous coronary intervention: A randomized study. *J Am Coll Cardiol* 2001; **38:** 1061–1069. PMID: 11583883
1272. Kinjo K, Sato H, Sato H, Ohnishi Y, Hishida E, Nakatani D, et al; Osaka Acute Coronary Insufficiency Study (OACIS) Group. Prognostic significance of atrial fibrillation/atrial flutter in patients with acute myocardial infarction treated with percutaneous coronary intervention. *Am J Cardiol* 2003; **92:** 1150–1154. PMID: 14609587
1273. Wong CK, White HD, Wilcox RG, Criger DA, Califf RM, Topol EJ et al. New atrial fibrillation after acute myocardial infarction independently predicts death: The GUSTO-III experience. *Am Heart J* 2000; **140:** 878–885. PMID: 11099991
1274. Pizzetti F, Turazza FM, Franzosi MG, Barlera S, Ledda A, Maggioni AP, et al; GISSI-3 Investigators. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: The GISSI-3 data. *Heart* 2001; **86:** 527–532. PMID: 11602545
1275. Ruwald AC, Bloch Thomsen PE, Gang U, Jørgensen RM, Huikuri HV, Jons C. New-onset atrial fibrillation predicts malignant arrhythmias in post-myocardial infarction patients: A Cardiac Arrhythmias and RIsk Stratification after acute Myocardial infarction (CARISMA) substudy. *Am Heart J* 2013; **166:** 855–863.e3. PMID: 24176441
1276. Grönefeld GC, Mauss O, Li YG, Klingenheben T, Hohnloser SH. Association between atrial fibrillation and appropriate implantable cardioverter defibrillator therapy: Results from a prospective study. *J Cardiovasc Electrophysiol* 2000; **11:** 1208–1214. PMID: 11083241
1277. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: A retrospective analysis of the SOLVD trials [Studies of Left Ventricular Dysfunction]. *J Am Coll Cardiol* 1998; **32:** 695–703. PMID: 9741514
1278. Eckart RE, Scoville SL, Campbell CL, Shry EA, Stajduhar KC, Potter RN, et al. Sudden death in young adults: A 25-year review of autopsies in military recruits. *Ann Intern Med* 2004; **141:** 829–834. PMID: 15583223
1279. Bagnall RD, Weintraub RG, Ingles J, Duflou J, Yeates L, Lam L, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med* 2016; **374:** 2441–2452. PMID: 27332903
1280. Ogawa S, Ayusawa M, Ihsii M, Ogino K, Saji T, NIshigaki K, et al. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS2013) (in Japanese). http://www.j-circ.or.jp/guideline/pdf/JCS2013_ogawas_h.pdf (accessed Dec 25, 2019).
1281. Makino N, Nakamura Y, Yashiro M, Kosami K, Matsubara Y, Ae R, et al. Nationwide epidemiologic survey of Kawasaki disease in Japan, 2015–2016. *Pediatr Int* 2019; **61:** 397–403. PMID: 30786118
1282. Tsuda E, Kamiya T, Kimura K, Ono Y, Echigo S. Coronary artery dilatation exceeding 4.0 mm during acute Kawasaki disease predicts a high probability of subsequent late intima–medial thickening. *Pediatr Cardiol* 2002; **23:** 9–14. PMID: 11922521
1283. Tsuda E, Kamiya T, Ono Y, Kimura K, Kurosaki K, Echigo S. Incidence of stenotic lesions predicted by acute phase changes in coronary arterial diameter during Kawasaki disease. *Pediatr Cardiol* 2005; **26:** 73–79. PMID: 15136903
1284. Tsuda E, Tsujii N, Hayama Y. Cardiac events and the maximum diameter of coronary artery aneurysms in Kawasaki disease. *J Pediatr* 2017; **188:** 70–74.e1. PMID: 28662948
1285. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, Tang A, Berry E, Tremoulet AH, et al. Coronary artery aneurysms in Kawasaki disease: Risk factors for progressive disease and adverse cardiac events in the US population. *J Am Heart Assoc* 2016; **5:** e003289. PMID: 27633390
1286. Miura M, Kobayashi T, Kaneko T, Ayusawa M, Fukazawa R, Fukushima N, et al; The Z-score Project 2nd Stage Study Group. Association of severity of coronary artery aneurysms in patients with Kawasaki Disease and risk of later coronary events. *JAMA Pediatr* 2018; **172:** e180030. PMID: 29507955
1287. Angelini P, Velasco JA, Flamm S. Coronary anomalies: Incidence, pathophysiology, and clinical relevance. *Circulation* 2002; **105:** 2449–2454. PMID: 12021235
1288. Echigo S, Ichikawa H, Ueno T, Kado H, Tomita H, Niwa K, et al. Guidelines for management and re-interventional therapy in patients with congenital heart disease long-term after initial repair (JCS2012) (in Japanese). http://www.j-circ.or.jp/guideline/pdf/JCS2012_echigo_h.pdf (accessed Dec 25, 2019).
1289. Prêtre R, Tamisier D, Bonhoeffer P, Mauriat P, Pouard P, Sidi D, et al. Results of the arterial switch operation in neonates with transposed great arteries. *Lancet* 2001; **357:** 1826–1830. PMID: 11410190
1290. Collins RT. Cardiovascular disease in Williams syndrome. *Circulation* 2013; **127:** 2125–2134. PMID: 23716381
1291. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group: A statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. *Circulation* 2006; **113:** 1905–1920. PMID: 16567564
1292. Wakabayashi R. Clinical implication of a simple exercise stress test which applies rebound vertical jumping (jump test). *J Jpn Pediar Soc* 1987; **91:** 2974–2983 (in Japanese).
1293. Jan SL, Hwang B, Fu YC, Lee PC, Kao CH, Liu RS, et al. Comparison of 201Tl SPET and treadmill exercise testing in patients with Kawasaki disease. *Nucl Med Commun* 2000; **21:** 431–435. PMID: 10874699
1294. Fukuda T, Akagi T, Ishibashi M, Inoue O, Sugimura T, Kato H. Noninvasive evaluation of myocardial ischemia in Kawasaki disease: Comparison between dipyridamole stress thallium imaging and exercise stress testing. *Am Heart J* 1998; **135:** 482–487. PMID: 9506334
1295. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: A Scientific Statement for Health Professionals from the American Heart Association. *Circulation* 2017; **135:** e927–e999. PMID: 28356445
1296. Kobayashi T, Fuse S, Sakamoto N, Mikami M, Ogawa S,

Hamaoka K, et al; Z Score Project Investigators. A new Z score curve of the coronary arterial internal diameter using the Lambda–Mu–Sigma method in a pediatric population. *J Am Soc Echocardiogr* 2016; **29:** 794–801.e29. PMID: 27288089
1297. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, et al; Pediatric Heart Network Investigators. Coronary artery involvement in children with Kawasaki disease: Risk factors from analysis of serial normalized measurements. *Circulation* 2007; **116:** 174–179. PMID: 17576863
1298. Cifra B, Dragulescu A, Border WL, Mertens L. Stress echocardiography in paediatric cardiology. *Eur Heart J Cardiovasc Imaging* 2015; **16:** 1051–1059. PMID: 26130262
1299. Hui L, Chau AK, Leung MP, Chiu CS, Cheung YF. Assessment of left ventricular function long term after arterial switch operation for transposition of the great arteries by dobutamine stress echocardiography. *Heart* 2005; **91:** 68–72. PMID: 15604338
1300. Noto N, Ayusawa M, Karasawa K, Yamaguchi H, Sumitomo N, Okada T, et al. Dobutamine stress echocardiography for detection of coronary artery stenosis in children with Kawasaki disease. *J Am Coll Cardiol* 1996; **27:** 1251–1256. PMID: 8609352
1301. Noto N, Kamiyama H, Karasawa K, Ayusawa M, Sumitomo N, Okada T, et al. Long-term prognostic impact of dobutamine stress echocardiography in patients with Kawasaki disease and coronary artery lesions: A 15-year follow-up study. *J Am Coll Cardiol* 2014; **63:** 337–344. PMID: 24140657
1302. Kondo C. Myocardial perfusion imaging in pediatric cardiology. *Ann Nucl Med* 2004; **18:** 551–561. PMID: 15586628
1303. Karasawa K, Miyashita M, Taniguchi K, Kanamaru H, Ayusawa M, Noto N, et al. Detection of myocardial contractile reserve by low-dose dobutamine quantitative gated single-photon emission computed tomography in patients with Kawasaki disease and severe coronary artery lesions. *Am J Cardiol* 2003; **92:** 865–868. PMID: 14516896
1304. Zhang HL, Li SJ, Wang X, Yan J, Hua ZD. Preoperative evaluation and midterm outcomes after the surgical correction of anomalous origin of the left coronary artery from the pulmonary artery in 50 infants and children. *Chin Med J* 2017; **130:** 2816–2822. PMID: 29176139
1305. Kanamaru H, Karasawa K, Ichikawa R, Matsumura M, Miyashita M, Taniguchi K, et al. Dual myocardial scintigraphy mismatch in an infant with Bland-White-Garland syndrome. *Int J Cardiol* 2009; **135:** e1–e3. PMID: 18597871
1306. Reddy A, Bisoi AK, Singla S, Patel CD, Das S. Adenosine stress myocardial perfusion scintigraphy in pediatric patients after arterial switch operation. *Indian J Nucl Med* 2013; **28:** 210–215. PMID: 24379530
1307. Tsuda T, Bhat AM, Robinson BW, Baffa JM, Radtke W. Coronary artery problems late after arterial switch operation for transposition of the great arteries. *Circ J* 2015; **79:** 2372–2379. PMID: 26289969
1308. Koizumi K, Masaki H, Matsuda H, Uchiyama M, Okuno M, Oguma E, et al. Japanese consensus guidelines for pediatric nuclear medicine. Part 1: Pediatric radiopharmaceutical administered doses (JSNM pediatric dosage card). Part 2: Technical considerations for pediatric nuclear medicine imaging procedures. *Ann Nucl Med* 2014; **85:** 498–503. PMID: 24647992
1309. Dorfman AL, Fazel R, Einstein AJ, Applegate KE, Krumholz HM, Wang Y, et al. Use of medical imaging procedures with ionizing radiation in children: A population-based study. *Arch Pediatr Adolesc Med* 2011; **165:** 458–464. PMID: 21199972
1310. Karasawa K, Kamiyama H, Hashimoto T, Koizumi K. Survey questionnaire of pediatric nuclear medicine examinations in 14 Japanese institutes. *Kaku Igaku* 2013; **50:** 61–67 (in Japanese). PMID: 23855248
1311. Mettler FA Jr, Bhargavan M, Faulkner K, Gilley DB, Gray JE, Ibbott GS, et al. Radiologic and nuclear medicine studies in the United States and worldwide: Frequency, radiation dose, and comparison with other radiation sources: 1950–2007. *Radiology* 2009; **253:** 520–531. PMID: 19789227
1312. Karasawa K, Ayusawa M, Noto N, Yamaguchi H, Okada T, Harada K. The dobutamine stress Tl-201 myocardial single photon emission computed tomography for coronary artery stenosis caused by Kawasaki disease. *Pediatr Cardiol Card Surg* 1994; **9:** 723–733 (in Japanese).
1313. Prabhu AS, Singh TP, Morrow WR, Muzik O, Di Carli MF. Safety and efficacy of intravenous adenosine for pharmacologic stress testing in children with aortic valve disease or Kawasaki disease. *Am J Cardiol* 1999; **83:** 284–286. PMID: 10073840
1314. Karasawa K, Ayusawa M, Noto N, Sumitomo N, Okada T, Harada K. Optimum protocol of technetium-99 m tetrofosmin myocardial perfusion imaging for the detection of coronary stenosis lesions in Kawasaki disease. *J Cardiol* 1997; **30:** 331–339 (in Japanese). PMID: 9436075
1315. Monzen H, Hara M, Hirata M, Nakanishi A, Ogasawara M, Suzuki T, et al. Exploring a technique for reducing the influence of scattered rays from surrounding organs to the heart during myocardial perfusion scintigraphy with technetium-99 m sestamibi and technetium-99 m tetrofosmin. *Ann Nucl Med* 2006; **20:** 705–710. PMID: 17385311
1316. Johnson LL, Verdesca SA, Aude WY, Xavier RC, Nott LT, Campanella MW, et al. Postischemic stunning can affect left ventricular ejection fraction and regional wall motion on post-stress gated sestamibi tomograms. *J Am Coll Cardiol* 1997; **30:** 1641–1648. PMID: 9385888
1317. Ishikawa Y, Fujiwara M, Ono Y, Tsuda E, Matsubara T, Furukawa S, et al. Exercise- or dipyridamole-loaded QGS is useful to evaluate myocardial ischemia and viability in the patients with a history of Kawasaki disease. *Pediatr Int* 2005; **47:** 505–511. PMID: 16190955
1318. JCS Joint Working Group. Guidelines for drug therapy in pediatric patients with cardiovascular diseases (JCS 2012). *Circ J* 2014; **78:** 507–533. PMID: 24369273
1319. Watanabe H, Kamiyama H, Kato M, Komori A, Abe Y, Ayusawa M. Appropriate use of a beta-blocker in paediatric coronary CT angiography. *Cardiol Young* 2018; **28:** 1148–1153. PMID: 30079850
1320. Dietz SM, Tacke CE, Kuipers IM, Wiegman A, de Winter RJ, Burns JC, et al. Cardiovascular imaging in children and adults following Kawasaki disease. *Insights Imaging* 2015; **6:** 697–705. PMID: 26210915
1321. Kanamaru H, Karasawa K, Ichikawa R, Abe O, Miyashita M, Taniguchi K, et al. Advantages of multislice spiral computed tomography for evaluation of serious coronary complications after Kawasaki disease. *J Cardiol* 2007; **50:** 21–27 (in Japanese). PMID: 17685026
1322. Singhal M, Gupta P, Singh S, Khandelwal N. Computed tomography coronary angiography for evaluation of children with Kawasaki disease. *Curr Probl Diagn Radiol* 2018; **47:** 238–244. PMID: 29203262
1323. Singh S, Singh N, Gulati GS, Ramakrishnan S, Kumar G, Sharma S, et al. Dual-source computed tomography for chronic total occlusion of coronary arteries. *Catheter Cardiovasc Interv* 2016; **88:** E117–E125. PMID: 24740894
1324. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate use criteria for cardiac computed tomography: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *Circulation* 2010; **122:** e525–e555. PMID: 20975004
1325. Cademartiri F, La Grutta L, Malagò R, Alberghina F, Meijboom WB, Pugliese F, et al. Prevalence of anatomical variants and coronary anomalies in 543 consecutive patients studied with 64-slice CT coronary angiography. *Eur Radiol* 2008; **18:** 781–791. PMID: 18246357
1326. Angelini P. Coronary artery anomalies: An entity in search of an identity. *Circulation* 2007; **115:** 1296–1305. PMID: 17353457
1327. Soliman M, Laxer R, Manson D, Yeung R, Doria AS. Imaging of systemic vasculitis in childhood. *Pediatr Radiol* 2015; **45:** 1110–1125. PMID: 26198677
1328. Kohout A, Steiner I, Zákravská N. Coronary arteritis with marked fibrous periarteritis: Case report. *Cardiovasc Pathol* 2000; **9:** 297–299. PMID: 11064278
1329. Ghoshhajra BB, Lee AM, Engel LC, Celeng C, Kalra MK, Brady TJ, et al. Radiation dose reduction in pediatric cardiac computed tomography: Experience from a tertiary medical center. *Pediatr Cardiol* 2014; **35:** 171–179. PMID: 23872908
1330. Kanamaru H, Kimijima S, Mugishima H. Pediatric cardiac computed tomography: Focusing on pediatric coronary computed tomographic angiography. *J Jpn Soc Pediatr Radiol* 2011; **27:** 106–117 (in Japanese).
1331. Deak PD, Smal Y, Kalender WA. Multisection CT protocols: Sex- and age-specific conversion factors used to determine effec-

tive dose from dose-length product. *Radiology* 2010; **257:** 158–166. PMID: 20851940
1332. Lee SE, Lin FY, Lu Y, Chang HJ, Min JK. Rationale and design of the coronary computed tomographic angiography for selective cardiac catheterization: Relation to cardiovascular outcomes, cost effectiveness and quality of life (CONSERVE) trial. *Am Heart J* 2017; **186:** 48–55. PMID: 28454832
1333. Rajiah P, Setser RM, Desai MY, Flamm SD, Arruda JL. Utility of free-breathing, whole-heart, three-dimensional magnetic resonance imaging in the assessment of coronary anatomy for congenital heart disease. *Pediatr Cardiol* 2011; **32:** 418–425. PMID: 21210094
1334. Tangcharoen T, Bell A, Hegde S, Hussain T, Beerbaum P, Schaeffter T, et al. Detection of coronary artery anomalies in infants and young children with congenital heart disease by using MR imaging. *Radiology* 2011; **259:** 240–247. PMID: 21325034
1335. Beerbaum P, Sarikouch S, Laser KT, Greil G, Burchert W, Körperich H. Coronary anomalies assessed by whole-heart isotropic 3D magnetic resonance imaging for cardiac morphology in congenital heart disease. *J Magn Reson Imaging* 2009; **29:** 320–327. PMID: 19161183
1336. Takemura A, Suzuki A, Inaba R, Sonobe T, Tsuchiya K, Omuro M, et al. Utility of coronary MR angiography in children with Kawasaki disease. *AJR Am J Roentgenol* 2007; **188:** W534–W539. PMID: 17515343
1337. Taylor AM, Dymarkowski S, Hamaekers P, Razavi R, Gewillig M, Mertens L, et al. MR coronary angiography and late-enhancement myocardial MR in children who underwent arterial switch surgery for transposition of great arteries. *Radiology* 2005; **234:** 542–547. PMID: 15591430
1338. Mavrogeni S, Papadopoulos G, Douskou M, Kaklis S, Seimenis I, Varlamis G, et al. Magnetic resonance angiography, function and viability evaluation in patients with Kawasaki disease. *J Cardiovasc Magn Reson* 2006; **8:** 493–498. PMID: 16758550
1339. Greil GF, Seeger A, Miller S, Claussen CD, Hofbeck M, Botnar RM, et al. Coronary magnetic resonance angiography and vessel wall imaging in children with Kawasaki disease. *Pediatr Radiol* 2007; **37:** 666–673. PMID: 17541574
1340. Tacke CE, Kuipers IM, Groenink M, Spijkerboer AM, Kuijpers TW. Cardiac magnetic resonance imaging for noninvasive assessment of cardiovascular disease during the follow-up of patients with Kawasaki disease. *Circ Cardiovasc Imaging* 2011; **4:** 712–720. PMID: 21921132
1341. Kim JW, Goo HW. Coronary artery abnormalities in Kawasaki disease: Comparison between CT and MR coronary angiography. *Acta Radiol* 2013; **54:** 156–163. PMID: 23482350
1342. Hussain T, Mathur S, Peel SA, Valverde I, Bilska K, Henningsson M, et al. Coronary artery size and origin imaging in children: A comparative study of MRI and trans-thoracic echocardiography. *BMC Med Imaging* 2015; **15:** 48. PMID: 26502883
1343. Silva Vieira M, Henningsson M, Dedieu N, Vassiliou VS, Bell A, Mathur S, et al. Improved coronary magnetic resonance angiography using gadobenate dimeglumine in pediatric congenital heart disease. *Magn Reson Imaging* 2018; **49:** 47–54. PMID: 29339139
1344. Kiaos A, Tziatzios I, Hadjimiltiades S, Karvounis C, Karamitsos TD. Diagnostic performance of stress perfusion cardiac magnetic resonance for the detection of coronary artery disease: A systematic review and meta-analysis. *Int J Cardiol* 2018; **252:** 229–233. PMID: 29196090
1345. Vijarnsorn C, Noga M, Schantz D, Pepelassis D, Tham EB. Stress perfusion magnetic resonance imaging to detect coronary artery lesions in children. *Int J Cardiovasc Imaging* 2017; **33:** 699–709. PMID: 28000002
1346. Etesami M, Gilkeson RC, Rajiah P. Utility of late gadolinium enhancement in pediatric cardiac MRI. *Pediatr Radiol* 2016; **46:** 1096–1113. PMID: 26718199
1347. Sarikouch S, Peters B, Gutberlet M, Leismann B, Kelter-Kloepping A, Koerperich H, et al. Sex-specific pediatric percentiles for ventricular size and mass as reference values for cardiac MRI: Assessment by steady-state free-precession and phase-contrast MRI flow. *Circ Cardiovasc Imaging* 2010; **3:** 65–76. PMID: 19820203
1348. Windram J, Grosse-Wortmann L, Shariat M, Greer ML, Crawford MW, Yoo SJ. Cardiovascular MRI without sedation or general anesthesia using a feed-and-sleep technique in neonates and infants. *Pediatr Radiol* 2012; **42:** 183–187. PMID: 21861089
1349. Fogel MA, Weinberg PM, Parave E, Harris C, Montenegro L, Harris MA, et al. Deep sedation for cardiac magnetic resonance imaging: A comparison with cardiac anesthesia. *J Pediatr* 2008; **152:** 534–539.e1. PMID: 18346511
1350. The Japan Pediatric Society, the Japanese Society of Pediatric Anesthesiology, Japanese Society of Pediatric Radiology. Joint proposal on pediatric sedation for MRI examinations (in Japanese). https://www.jpeds.or.jp/uploads/files/20150129.pdf (accessed Dec 25, 2019).
1351. Odegard KC, DiNardo JA, Tsai-Goodman B, Powell AJ, Geva T, Laussen PC. Anaesthesia considerations for cardiac MRI in infants and small children. *Paediatr Anaesth* 2004; **14:** 471–476. PMID: 15153209
1352. Stockton E, Hughes M, Broadhead M, Taylor A, McEwan A. A prospective audit of safety issues associated with general anesthesia for pediatric cardiac magnetic resonance imaging. *Paediatr Anaesth* 2012; **22:** 1087–1093. PMID: 22458837
1353. Sarikouch S, Schaeffler R, Körperich H, Dongas A, Haas NA, Beerbaum P. Cardiovascular magnetic resonance imaging for intensive care infants: Safe and effective? *Pediatr Cardiol* 2009; **30:** 146–152. PMID: 18709400
1354. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: A retrospective cohort study. *Lancet* 2012; **380:** 499–505. PMID: 22681860
1355. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: Data linkage study of 11 million Australians. *BMJ* 2013; **346:** f2360. PMID: 23694687
1356. Shellock FG, Spinazzi A. MRI safety update 2008: Part 2 screening patients for MRI. *AJR Am J Roentgenol* 2008; **191:** 1140–1149. PMID: 18806156
1357. Runge VM. Safety of approved MR contrast media for intravenous injection. *J Magn Reson Imaging* 2000; **12:** 205–213. PMID: 10931582
1358. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing IV contrast media in children and adults. *AJR Am J Roentgenol* 2007; **189:** 1533–1538. PMID: 18029897
1359. Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. *AJR Am J Roentgenol* 2011; **196:** W138–W143. PMID: 21257854
1360. Kaewlai R, Abujudeh H. Nephrogenic systemic fibrosis. *AJR Am J Roentgenol* 2012; **199:** W17–W23. PMID: 22733927
1361. Sadowski EA, Bennett LK, Chan MR, Wentland AL, Garrett AL, Garrett RW, et al. Nephrogenic systemic fibrosis: Risk factors and incidence estimation. *Radiology* 2007; **243:** 148–157. PMID: 17267695
1362. Mendichovszky IA, Marks SD, Simcock CM, Olsen OE. Gadolinium and nephrogenic systemic fibrosis: Time to tighten practice. *Pediatr Radiol* 2008; **38:** 489–496. PMID: 17943276
1363. Kanda T, Fukusato T, Matsuda M, Toyoda K, Oba H, Kotoku J, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: Evaluation of autopsy brain specimens with inductively coupled plasma mass apectroscopy. *Radiology* 2015; **276:** 228–232. PMID: 25942417
1364. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology* 2015; **275:** 772–782. PMID: 25742194
1365. Murata N, Gonzalez-Cuyar LF, Murata K, Fligner C, Dills R, Hippe D, et al. Macrocyclic and other non-group 1 gadolinium contrast agents deposit low levels of gadolinium in brain and bone tissue: Preliminary results from 9 patients with normal renal function. *Invest Radiol* 2016; **51:** 447–453. PMID: 26863577
1366. Welk B, McArthur E, Morrow SA, MacDonald P, Hayward J, Leung A, et al. Association between gadolinium contrast exposure and the risk of Parkinsonism. *JAMA* 2016; **316:** 96–98. PMID: 27380348
1367. European Medicines Agency (EMA). EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans. https://www.ema.europa.eu/en/news/emas-final-opinion-confirms-restrictions-use-linear-gadolinium-agents-body-scans (accessed Dec 25, 2019).
1368. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs;

review to continue. https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm (accessed Dec 25, 2019).
1369. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings. https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm (accssed in Dec 25, 2019).
1370. Radomskij P, Schmidt MA, Heron CW, Prasher D. Effect of MRI noise on cochlear function. *Lancet* 2002; **359:** 1485. PMID: 11988249
1371. Kussman BD, Mulkern RV, Holzman RS. Iatrogenic hyperthermia during cardiac magnetic resonance imaging. *Anesth Analg* 2004; **99:** 1053–1055. PMID: 15385349
1372. Ohkubo T, Fukazawa R, Ikegami E, Ogawa S. Reduced shear stress and disturbed flow may lead to coronary aneurysm and thrombus formations. *Pediatr Int* 2007; **49:** 1–7. PMID: 17250496
1373. Ogawa S, Ohkubo T, Fukazawa R, Kamisago M, Kuramochi Y, Uchikoba Y, et al. Estimation of myocardial hemodynamics before and after intervention in children with Kawasaki disease. *J Am Coll Cardiol* 2004; **43:** 653–661. PMID: 14975478
1374. Mitani Y, Ohashi H, Sawada H, Ikeyama Y, Hayakawa H, Takabayashi S, et al. In vivo plaque composition and morphology in coronary artery lesions in adolescents and young adults long after Kawasaki disease: A virtual histology–intravascular ultrasound study. *Circulation* 2009; **119:** 2829–2836. PMID: 19451352
1375. Dionne A, Ibrahim R, Gebhard C, Bakloul M, Selly JB, Leye M, et al. Coronary wall structural changes in patients with Kawasaki disease: New insights from optical coherence tomography (OCT). *J Am Heart Assoc* 2015; **4:** E001939. PMID: 25991013
1376. Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, et al; CRUSADE Investigators. Prior polyvascular disease: Risk factor for adverse ischaemic outcomes in acute coronary syndromes. *Eur Heart J* 2009; **30:** 1195–1202. PMID: 19339264
1377. Ohman EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liau CS, et al; REACH Registry Investigators. The REduction of Atherothrombosis for Continued Health (REACH) Registry: An international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J* 2006; **151:** 786.e1–786.e10. PMID: 16569533
1378. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al; REACH Registry Investigators. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; **295:** 180–189. PMID: 16403930
1379. Yamazaki T, Goto S, Shigematsu H, Shimada K, Uchiyama S, Nagai R, et al; REACH Registry Investigators. Prevalence, awareness and treatment of cardiovascular risk factors in patients at high risk of atherothrombosis in Japan. *Circ J* 2007; **71:** 995–1003. PMID: 17587702
1380. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al; REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010; **304:** 1350–1357. PMID: 20805624
1381. Ministry of Health, Labor and Welfare. 2016 demographic statistics (in Japanese). http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei16/dL/10_h6.pdf, p15 (accessed Dec 25, 2019).
1382. Ministry of Health, Labor and Welfare. Overview of the 2016 basic survey on national life (in Japanese). https://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa16/dL/05.pdf, p 29 (accessed Dec 25, 2019).
1383. Ducrocq G, Amarenco P, Labreuche J, Alberts MJ, Mas JL, Ohman EM, et al. A history of stroke/transient ischemic attack indicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. *Circulation* 2013; **127:** 730–738. PMID: 23277306
1384. Kitaoka M, Matsuo H, Taniguchi N, Ozaki T, Kaneda S, Tooda E, et al;The Japan Society of Ultrasonics in Medicine. Standard method for ultrasound evaluation of carotid artery lesions. *Jpn J Med Ultrasonics* 2009; **36:** 501–518 (in Japanese). https://www.jsum.or.jp/committee/diagnostic/pdf/36-4.pdf (accessed Dec 25, 2019).
1385. Chappell FM, Wardlaw JM, Young GR, Gillard JH, Roditi GH, Yip B, et al. Carotid artery stenosis: Accuracy of noninvasive tests: Individual patient data meta-analysis. *Radiology* 2009; **251:** 493–502. PMID: 19276319
1386. Moody AR, Murphy RE, Morgan PS, Martel AL, Delay GS, Allder S, et al. Characterization of complicated carotid plaque with magnetic resonance direct thrombus imaging in patients with cerebral ischemia. *Circulation* 2003; **107:** 3047–3052. PMID: 12796133
1387. Kaufmann TJ, Huston J 3rd, Mandrekar JN, Schleck CD, Thielen KR, Kallmes DF. Complications of diagnostic cerebral angiography: Evaluation of 19,826 consecutive patients. *Radiology* 2007; **243:** 812–819. PMID: 17517935
1388. Bendszus M, Koltzenburg M, Burger R, Warmuth-Metz M, Hofmann E, Solymosi L. Silent embolism in diagnostic cerebral angiography and neurointerventional procedures: A prospective study. *Lancet* 1999; **354:** 1594–1597. PMID: 10560674
1389. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg* 2007; **33**(Suppl)**:** S1–S75. PMID: 17140820
1390. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017; **135:** e726–e779. PMID: 27840333
1391. Miyata T, Akishita M, Azuma N, Kichikawa K, Goto N, Komori K, et al. JCS Joint Working Group: Guidelines for the management of peripheral arterial occlusive diseases (JCS 2015) (in Japanese). http://www.j-circ.or.jp/guideline/pdf/JCS2015_miyata_h.pdf (accessed Dec 25, 2019).
1392. The Japan Radiological Society. The Japanese imaging guideline 2016. Tokyo: Kanehara & Co. Ltd., 2016; 239–253 (in Japanese).
1393. Ota H, Takase K, Igarashi K, Chiba Y, Haga K, Saito H, et al. MDCT compared with digital subtraction angiography for assessment of lower extremity arterial occlusive disease: Importance of reviewing cross-sectional images. *AJR Am J Roentgenol* 2004; **182:** 201–209. PMID: 14684540
1394. Met R, Bipat S, Legemate DA, Reekers JA, Koelemay MJ. Diagnostic performance of computed tomography angiography in peripheral arterial disease: A systematic review and meta-analysis. *JAMA* 2009; **301:** 415–424. PMID: 19176443
1395. Suzuki M, Tanaka R, Yoshioka K, Abiko A, Ehara S. Subtraction CT angiography for the diagnosis of iliac arterial stenoocclusive disease. *Jpn J Radiol* 2016; **34:** 194–202. PMID: 26682737
1396. Sommer WH, Johnson TR, Becker CR, Arnoldi E, Kramer H, Reiser MF, et al. The value of dual-energy bone removal in maximum intensity projections of lower extremity computed tomography angiography. *Invest Radiol* 2009; **44:** 285–292. PMID: 19346965
1397. Kau T, Eicher W, Reiterer C, Niedermayer M, Rabitsch E, Senft B, et al. Dual-energy CT angiography in peripheral arterial occlusive disease-accuracy of maximum intensity projections in clinical routine and subgroup analysis. *Eur Radiol* 2011; **21:** 1677–1686. PMID: 21365195
1398. Loewe C, Schoder M, Rand T, Hoffmann U, Sailer J, Kos T et al. Peripheral vascular occlusive disease: Evaluation with contrast-enhanced moving-bed MR angiography versus digital subtraction angiography in 106 patients. *AJR Am J Roentgenol* 2002; **179:** 1013–1021. PMID: 12239057
1399. Agarwal R, Brunelli SM, Williams K, Mitchell MD, Feldman HI, Umscheid CA. Gadolinium-based contrast agents and nephrogenic systemic fibrosis: A systematic review and meta-analysis. *Nephrol Dial Transplant* 2009; **24:** 856–863. PMID: 18952698
1400. Lim RP, Hecht EM, Xu J, Babb JS, Oesingmann N, Wong S et al. 3D nongadolinium-enhanced ECG-gated MRA of the distal lower extremities: Preliminary clinical experience. *J Magn Reson Imaging* 2008; **28:** 181–189. PMID: 18581339
1401. Yi CY, Zhou DX, Li HH, Wang Y, Chen K, Chen J, et al. Comparison of imaging value for diabetic lower extremity arterial disease between FBI and CE-MRA. *Eur Rev Med Pharmacol Sci* 2016; **20:** 3078–3086. PMID: 27460738

## Appendix 1. Details of Members

**Chairs**
- Nagara Tamaki, Department of Radiology, Kyoto Prefectural University of Medicine Graduate School
- Masakazu Yamagishi, Osaka University of Human Science

**Members**
- Takashi Akasaka, Department of Cardiovascular Medicine, Wakayama Medical University
- Taishiro Chikamori, Department of Cardiology, Tokyo Medical University
- Hiroyuki Daida, Department of Cardiovascular Medicine, Juntendo University Graduate School
- Nobusada Funabashi, Department of Cardiovascular Medicine, Chiba University Graduate School
- Atsushi Hirayama, Department of Cardiology, Osaka Police Hospital
- Takanori Ikeda, Department of Cardiovascular Medicine, Toho University Graduate School
- Masahiro Jinzaki, Department of Radiology, Keio University School of Medicine
- Yasuki Kihara, Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical and Health Sciences
- Kazuo Kimura, Division of Cardiology, Yokohama City University Medical Center
- Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School
- Shinichiro Kumita, Department of Radiology, Nippon Medical School
- Yoshiki Kusama, Department of Internal Medicine, Honjo General Hospital
- Masaru Miura, Department of Cardiology, Tokyo Metropolitan Children's Medical Center
- Teruhito Mochizuki, Department of Radiology, Ehime University Graduate School
- Kenichi Nakajima, Department of Functional Imaging and Artificial Intelligence, Kanazawa Universtiy
- Tomoaki Nakata, Department of Cardiology, Hakodate Goryokaku Hospital
- Satoshi Nakatani, Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School of Medicine
- Koichi Node, Department of Cardiovascular Medicine, Saga University
- Akihiko Nogami, Department of Cardiology, University of Tsukuba
- Atsushi Nohara, Division of Clinical Genetics, Ishikawa Prefectural Central Hospital
- Yutaka Otsuji, Second Department of Internal Medicine, University of Occupational and Environmental Health, Japan
- Hajime Sakuma, Department of Radiology, Mie University Graduate School
- Hiroshi Tada, Department of Cardiovascular Medicine, University of Fukui
- Yasuchika Takeishi, Department of Cardiovascular Medicine, Fukushima Medical University
- Kunihiko Teraoka, Department of Internal Medicine, Sakakibara Memorial Clinic
- Kenichi Tsujita, Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University
- Shiro Uemura, Department of Cardiology, Kawasaki Medical School
- Kenji Ueshima, Center for Accessing Early Promising Treatment, Kyoto University Hospital
- Hiroyoshi Yokoi, Cardiovascular Center, Fukuoka Sanno Hospital
- Kunihiro Yoshioka, Department of Radiology, Iwate Medical University
- Masafumi Watanabe, Department of Cardiology, Pulmonology, and Nephrology, Yamagata University

**Collaborators**
- Toshihiko Asanuma, Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School
- Daisuke Fukamachi, Department of Cardiology, Nihon University Itabashi Hospital
- Akiyoshi Hashimoto, Department of Cardiovascular, Renal and Metabolic Medicine, Sapporo Medical University
- Kenshi Hayashi, Department of Cardiovascular Medicine, Kanazawa University Hospital
- Masahiro Higashi, Department of Radiology, National Hospital Organization Osaka National Hospital
- Takafumi Hiro, Division of Cardiology, Department of Medicine, Nihon University
- Yuichi Ishikawa, Department of Pediatric Cardiology, Fukuoka Children's Hospital
- Koichi Kaikita, Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University
- Hiroshi Kamiyama, Department of Pediatrics and Child Health, Nihon University
- Tokuo Kasai, Department of Cardiology, Uonuma Kinen Hospital
- Eri Kato, Department of Cardiovascular Medicine, Department of Clinical Laboratory, Kyoto University Hospital
- Masaaki Kawashiri, Department of Cardiovascular and Internal Medicine, Kanazawa University
- Teruhito Kido, Department of Radiology, Ehime University Graduate School
- Toshio Kinoshita, Department of Cardiovascular Medicine, Toho University
- Tomonari Kiriyama, Department of Radiology, Nippon Medical School
- Keisuke Kiso, Department of Diagnostic Radiology, Tohoku University Hospital
- Kakuya Kitagawa, Department of Advanced Diagnostic Imaging, Mie University Graduate School
- Eitaro Kodani, Department of Internal Medicine and Cardiology, Nippon Medical School Tama Nagayama Hospital
- Masami Kosuge, Division of Cardiology, Yokohama City University Medical Center
- Teruyoshi Kume, Department of Cardiology, Kawasaki Medical School
- Akira Kurata, Department of Radiology, Ehime University Graduate School
- Satoshi Kurisu, Department of Cardiovascular Medicine, Hiroshima University Graduate School of Biomedical and Health Sciences
- Naoya Matsumoto, Division of Cardiology, Department of Medicine, Nihon University
- Hitoshi Matsuo, Department of Cardiovascular Medicine, Gifu Heart Center
- Masao Miyagawa, Department of Radiology, Ehime University Hospital
- Katsumi Miyauchi, Department of Cardiovascular Medicine, Juntendo University
- Takehiro Nakahara, Department of Radiology, Keio University School of Medicine
- Takuya Nakahashi, Department of Internal Medicine, Takaoka City Hospital
- Akihiro Nomura, Innovative Clinical Research Center, Kanazawa University Hospital
- Takahiro Ohara, Division of Community Medicine, Tohoku Medical and Pharmaceutical University
- Akira Sato, Department of Cardiology, University of Tsukuba
- Hiroki Shiomi, Department of Cardiovascular Medicine, Kyoto University Graduate School
- Yasutsugu Shiono, Department of Cardiovascular Medicine, Wakayama Medical University
- Junichi Taki, Department of Nuclear Medicine, Kanazawa University
- Masaaki Takeuchi, Department of Laboratory and Transfusion Medicine, Hospital of the University of Occupational and Environmental Health, Japan
- Atsushi Tanaka, Department of Cardiovascular Medicine, Saga University
- Nobuhiro Tanaka, Department of Cardiology, Tokyo Medical University Hachioji Medical Center
- Ryoichi Tanaka, Department of Reconstructive Oral and Maxillofacial Surgery, Iwate Medical University
- Yoshitake Yamada, Department of Radiology, Keio University School of Medicine
- Keiichiro Yoshinaga, Department of Diagnostic and Therapeutic Nuclear Medicine, Molecular Imaging at the National Institute of Radiological Sciences
- Hideki Wada, Department of Cardiology, Juntendo University Shizuoka Hospital
- Tetsu Watanabe, Department of Cardiology, Pulmonology, and Nephrology, Yamagata University

**Independent Assessment Committee**
- Shun Kohsaka, Department of Cardiology, Keio University School of Medicine
- Yukio Ozaki, Department of Cardiology, Fujita Medical University
- Wataru Shimizu, Department of Cardiovascular Medicine, Nippon Medical School
- Satoshi Yasuda, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine
- Hideaki Yoshino, Department of Cardiology, Kyorin University Hospital

(Listed in the order of the Japanese syllabary; affiliations as of November 2020)

## Appendix 2. Disclosure of Potential Conflicts of Interest (COI): JCS 2018 Guideline on Diagnosis of Chronic Coronary Heart Diseases

| Author | Potential COI of the participant | | | | | | | | | Potential COI of the marital partner, firstdegree family members, or those who share income and property | Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Employer/ leadership position (private company) | Stake-holder | Patent royalty | Honorarium | Payment for manuscripts | Research grant | Scholarship (educational) grant | Endowed chair | Other rewards | | Research grant | Scholarship (educational) grant |
| Chairs:<br>Masakazu Yamagishi | | | | Amgen Astellas BioPharma K.K.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co., Ltd. | | MSD K.K. | Astellas Pharma Inc.<br>Abbott Vascular Japan Co., Ltd.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Shionogi & Co., Ltd.<br>FUJI YAKUHIN CO., LTD.<br>Ono Pharmaceutical Co., Ltd.<br>Otsuka Pharmaceutical Co., Ltd.<br>Teijin Pharma Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Takeda Pharmaceutical Company Limited | | | | | |
| Chairs:<br>Nagara Tamaki | | | | Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM RI Pharma Co., Ltd. | | | | | | | | |
| Members:<br>Takashi Akasaka | | | | Amgen Astellas BioPharma K.K.<br>Abbott Vascular Japan Co., Ltd.<br>St. Jude Medical Japan Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co., Ltd. | | Daiichi Sankyo Company, Limited<br>Infraredx, Inc. | ACIST Medical Systems<br>Astellas Pharma Inc.<br>St. Jude Medical Japan Co., Ltd.<br>Novartis Pharma K.K.<br>HeartFlow Japan G.K.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Daiichi Sankyo Company, Limited | Abbott Vascular Japan Co., Ltd.<br>TERUMO CORPORATION<br>Goodman Co.,LTD.<br>St. Jude Medical Japan Co., Ltd.<br>Boston Scientific Corporation | | | | |
| Members:<br>Takanori Ikeda | | | | Bayer Yakuhin, Ltd.<br>Ono Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Bristol-Myers Squibb<br>Pfizer Japan Inc.<br>Boehringer Ingelheim GmbH | | Boston Scientific Corporation | Daiichi Sankyo Company, Limited<br>Medtronic Japan Co., Ltd.<br>Japan Lifeline Co.,Ltd. | | | | | |
| Members:<br>Kenji Ueshima | | | | Site Support Institute Co., Ltd. | | | | | | | | |
| Members:<br>Shiro Uemura | | | | Amgen Astellas BioPharma K.K.<br>Abbott Vascular Japan Co., Ltd.<br>Sanofi K.K.<br>TERUMO CORPORATION<br>Bayer Yakuhin, Ltd.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co ., Ltd. | | | Astellas Pharma Inc.<br>Abbott Vascular Japan Co., Ltd.<br>Sanofi K.K.<br>TERUMO CORPORATION<br>Bayer Yakuhin, Ltd.<br>Boston Scientific Corporation<br>Shionogi & Co., Ltd.<br>Goodman Co.,LTD.<br>Otsuka Pharmaceutical Co., Ltd.<br>Sumitomo Dainippon Pharma Co., Ltd.<br>Daiichi Sankyo Company, Limited | | | | | |
| Members:<br>Yutaka Otsuji | | | | | | Fukuda Life Tech Co. Ltd. | MSD K.K.<br>Astellas Pharma Inc.<br>Abbott Vascular Japan Co., Ltd.<br>Novartis Pharma K.K.<br>Boston Scientific Corporation<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Takeda Pharmaceutical Company Limited | | | | | |

| Author | Potential COI of the participant | | | | | | | | | Potential COI of the marital partner, firstdegree family members, or those who share income and property | Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Employer/ leadership position (private company) | Stake-holder | Patent royalty | Honorarium | Payment for manuscripts | Research grant | Scholarship (educational) grant | Endowed chair | Other rewards | | Research grant | Scholarship (educational) grant |
| Members:<br>Yasuki Kihara | | | | Actelion Pharmaceuticals Japan Ltd.<br>Bayer Yakuhin, Ltd.<br>Otsuka Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Teijin Home Healthcare Limited<br>Nippon Boehringer Ingelheim Co ., Ltd.<br>Takeda Pharmaceutical Company Limited | | Teijin Pharma Limited<br>EP-CRSU Co., Ltd. | MSD K.K.<br>Astellas Pharma Inc.<br>Sanofi K.K.<br>BIOTRONIK Japan, Inc.<br>Pfizer Japan Inc.<br>Boston Scientific Corporation<br>Akane-kai Tsuchiya Hospital<br>Federation of National Public Services and Affiliated Personnel Mutual Aid Associations Kure Kyosai Hospital<br>Otsuka Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Takeda Pharmaceutical Company Limited<br>Senoo Hospital | | | | | |
| Members:<br>Kazuo Kimura | | | | AstraZeneca K.K.<br>Sanofi K.K.<br>Bristol-Myers Squibb<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Daiichi Sankyo Company, Limited | | Otsuka Pharmaceutical Co., Ltd.<br>Bayer Yakuhin, Ltd.<br>Research Institute for Production Development<br>Japan Agency for Medical Research and Development<br>Sanofi K.K.<br>Japan Medical Association | Takeda Pharmaceutical Company Limited<br>Ono Pharmaceutical Co., Ltd.<br>MSD K.K.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Daiichi Sankyo Company, Limited | | | | | |
| Members:<br>Takeshi Kimura | | | | Abbott Vascular Japan Co., Ltd.<br>Sanofi K.K.<br>Bristol-Myers Squibb<br>Kowa Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co., Ltd. | | EP-CRSU Co., Ltd.<br>IQVIA Services Japan K.K.<br>Otsuka Pharmaceutical Co., Ltd.<br>EPS Corporation | Astellas Pharma Inc.<br>Boston Scientific Corporation<br>MID,Inc.<br>Otsuka Pharmaceutical Co., Ltd.<br>Sumitomo Dainippon Pharma Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Takeda Pharmaceutical Company Limited | | | | | |
| Members:<br>Yoshiki Kusama | | | | | | | Daiichi Sankyo Company, Limited<br>Bayer Yakuhin, Ltd. | | | | | |
| Members:<br>Shinichiro Kumita | | | | Nihon Medi-Physics Co.,Ltd. | | | | | | | | Eisai Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM RI Pharma Co., Ltd. |
| Members:<br>Hajime Sakuma | | | | Bayer Yakuhin, Ltd. | | | Eisai Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>FUJIFILM RI Pharma Co., Ltd.<br>Fuji Pharma Co., Ltd. | | | | | |
| Members:<br>Masahiro Jinzaki | | | | HeartFlow Japan G.K. | | Bayer Yakuhin, Ltd.<br>CANON MEDICAL SYSTEMS CORPORATION<br>GE Healthcare | Eisai Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>FUJIFILM RI Pharma Co., Ltd.<br>Fuji Pharma Co., Ltd. | Nihon Medi-Physics Co.,Ltd. | | | | |

| Author | Potential COI of the participant | | | | | | | | | Potential COI of the marital partner, firstdegree family members, or those who share income and property | Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Employer/ leadership position (private company) | Stake-holder | Patent royalty | Honorarium | Payment for manuscripts | Research grant | Scholarship (educational) grant | Endowed chair | Other rewards | | Research grant | Scholarship (educational) grant |
| Members:<br>Hiroyuki Daida | | | | MSD K.K.<br>Amgen Astellas BioPharma K.K.<br>Astellas Pharma Inc.<br>AstraZeneca K.K.<br>Sanofi K.K.<br>Bayer Yakuhin, Ltd.<br>Kowa Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Takeda Pharmaceutical Company Limited | | IQVIA Services Japan K.K.<br>St. Jude Medical Japan Co., Ltd.<br>Kowa Pharmaceutical Co., Ltd.<br>Sanwa Kagaku Kenkyusho Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>TOSHIBA MEDICAL SYSTEMS CORPORATION<br>Nihon Medi-Physics Co.,Ltd. | MSD K.K.<br>Actelion Pharmaceuticals Japan Ltd.<br>Astellas Pharma Inc.<br>Abbott Vascular Japan Co., Ltd.<br>Sanofi K.K.<br>St. Jude Medical Japan Co., Ltd.<br>Novartis Pharma K.K.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Shionogi & Co., Ltd.<br>Kowa Pharmaceutical Co., Ltd.<br>Otsuka Pharmaceutical Co., Ltd.<br>Sumitomo Dainippon Pharma Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Teijin Pharma Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Takeda Pharmaceutical Company Limited | Philips Respironics GK.<br>Fukuda Denshi Co., Ltd<br>ResMed | | | | |
| Members:<br>Yasuchika Takeishi | | | | Nippon Boehringer Ingelheim Co ., Ltd.<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>MSD K.K.<br>Sumitomo Dainippon Pharma Co., Ltd. | | CANON MEDICAL SYSTEMS CORPORATION<br>Tohoku Medical Systems<br>EVI JAPAN. INC. | MSD K.K.<br>Astellas Pharma Inc.<br>Bayer Yakuhin, Ltd.<br>Philips Respironics GK.<br>Otsuka Pharmaceutical Co., Ltd.<br>Sumitomo Dainippon Pharma Co., Ltd.<br>Teijin Pharma Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Nihon Medi-Physics Co.,Ltd.<br>Medtronic Japan Co., Ltd.<br>FUJIFILM RI Pharma Co., Ltd.<br>Takeda Pharmaceutical Company Limited | Actelion Pharmaceuticals Japan Ltd.<br>St. Jude Medical Japan Co., Ltd.<br>BIOTRONIK Japan, Inc.<br>Fukuda Life Tech Co. Ltd.<br>Fukuda Life Tech Minamitohoku Co. Ltd.<br>Fukuda Denshi Co., Ltd<br>Fukuda Denshi Minami-tohoku hanbai Co., Ltd | | | | |
| Members:<br>Hiroshi Tada | | | | Johnson & Johnson K.K.<br>BIOTRONIK Japan, Inc.<br>Bristol-Myers Squibb<br>Kowa Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Medtronic Japan Co., Ltd. | | | MSD K.K.<br>Astellas Pharma Inc.<br>Abbott Vascular Japan Co., Ltd.<br>Sanofi K.K.<br>CENTRAL MEDICAL Co., Ltd.<br>D-sense<br>DVx Inc.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Medtronic Japan Co., Ltd.<br>Takeda Pharmaceutical Company Limited | | | | | |
| Members:<br>Taishiro Chikamori | | | | Mitsubishi Tanabe Pharma Corporation | | Ono Pharmaceutical Co., Ltd.<br>Medtronic Japan Co., Ltd. | MSD K.K.<br>Bayer Yakuhin, Ltd.<br>Sumitomo Dainippon Pharma Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>FUJIFILM RI Pharma Co., Ltd.<br>Takeda Pharmaceutical Company Limited | St. Jude Medical Japan Co., Ltd. | | | | |

| Author | Potential COI of the participant | | | | | | | | | Potential COI of the marital partner, firstdegree family members, or those who share income and property | Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Employer/ leadership position (private company) | Stake-holder | Patent royalty | Honorarium | Payment for manuscripts | Research grant | Scholarship (educational) grant | Endowed chair | Other rewards | | Research grant | Scholarship (educational) grant |
| Members: Kenichi Tsujita | | | | MSD K.K.<br>Amgen Astellas BioPharma K.K.<br>Sanofi K.K.<br>Bayer Yakuhin, Ltd.<br>Kowa Pharmaceutical Co., Ltd.<br>Otsuka Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Takeda Pharmaceutical Company Limited | | AstraZeneca K.K.<br>Linical Co.,Ltd.<br>Sugi Bee Garden Co.,LTD.<br>TEIJIN HOME HEALTHCARE LIMITED<br>Japan Medical Device Technology Co., Ltd. | Cardinal Health Japan<br>MSD K.K.<br>ITI CO., LTD.<br>Astellas Pharma Inc.<br>Abbott Vascular Japan Co., Ltd.<br>Eisai Co., Ltd.<br>KANEKA MEDIX CORP.<br>Goodman Co.,LTD.<br>Sanofi K.K.<br>GM MEDICAL CO.,LTD.<br>St. Jude Medical Japan Co., Ltd.<br>TERUMO CORPORATION<br>Novartis Pharma K.K.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Fides-one,Inc.<br>Bristol-Myers Squibb<br>Boston Scientific Corporation<br>Shionogi & Co., Ltd.<br>Otsuka Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Chugai Pharmaceutical Co.,Ltd.<br>Mitsubishi Tanabe Pharma Corporation<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Medtronic Japan Co., Ltd.<br>Japan Lifeline Co.,Ltd.<br>Takeda Pharmaceutical Company Limited | | | | |
| Members: Kunihiko Teraoka | IKAROS PUBLICATIONS LTD. | | | | | | | | | IKAROS PUBLICATIONS LTD. | | |
| Members: Kenichi Nakajima | | | | FUJIFILM RI Pharma Co., Ltd.<br>Nihon Medi-Physics Co.,Ltd. | | FUJIFILM RI Pharma Co., Ltd.<br>Siemens Mecical Solutions, Inc.<br>Spectrum Dynamics Medical. Inc. | | | | | | |
| Members: Tomoaki Nakata | | | | MSD K.K.<br>Astellas Pharma Inc.<br>TOA EIYO LTD.<br>Bristol-Myers Squibb<br>TSUMURA & CO.<br>Otsuka Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM RI Pharma Co., Ltd.<br>Takeda Pharmaceutical Company Limited | Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM RI Pharma Co., Ltd. | | | | | | |
| Members: Satoshi Nakatani | | | | Edwards Lifesciences Corporation<br>Abbott Vascular Japan Co., Ltd. | | | | | | | | |
| Members: Akihiko Nogami | | | | Abbott Medical Japan L.L.C<br>Bristol-Myers Squibb<br>Daiichi Sankyo Company, Limited | | | | Johnson & Johnson K.K.<br>DVx Inc.<br>Medtronic Japan Co., Ltd. | | | | |

| Author | Potential COI of the participant | | | | | | | | | Potential COI of the marital partner, firstdegree family members, or those who share income and property | Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Employer/ leadership position (private company) | Stake-holder | Patent royalty | Honorarium | Payment for manuscripts | Research grant | Scholarship (educational) grant | Endowed chair | Other rewards | | Research grant | Scholarship (educational) grant |
| Members:<br>Koichi Node | | | | MSD K.K.<br>Amgen Astellas BioPharma K.K.<br>Astellas Pharma Inc.<br>AstraZeneca K.K.<br>Eli Lilly and Company<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Ono Pharmaceutical Co., Ltd.<br>Otsuka Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Eli Lilly Japan K.K.<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Takeda Pharmaceutical Company Limited | | Astellas Pharma Inc.<br>TERUMO CORPORATION<br>Bayer Yakuhin, Ltd.<br>Asahi Kasei Corporation.<br>Teijin Pharma Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Nippon Boehringer Ingelheim Co ., Ltd.<br>Eli Lilly and Company | Astellas Pharma Inc.<br>Bayer Yakuhin, Ltd.<br>Bristol-Myers Squibb<br>Daiichi Sankyo Company, Limited<br>Teijin Pharma Limited<br>Takeda Pharmaceutical Company Limited | | | | | |
| Members:<br>Atsushi Nohara | | | | Amgen Astellas BioPharma K.K.<br>Astellas Pharma Inc.<br>Aegerion Pharmaceuticals Inc.<br>Sanofi K.K. | | | | | | | | |
| Members:<br>Atsushi Hirayama | | | | Amgen Astellas BioPharma K.K.<br>Astellas Pharma Inc.<br>AstraZeneca K.K.<br>Sanofi K.K.<br>TOA EIYO LTD.<br>Bayer Yakuhin, Ltd.<br>Bristol-Myers Squibb<br>Sumitomo Dainippon Pharma Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co., Ltd. | | | | Active Medical Co.,Ltd.<br>Abbott Medical Japan L.L.C<br>St. Jude Medical Japan Co., Ltd.<br>Fukuda Denshi Co., Ltd<br>Hokushin Medical Co.,Ltd.<br>Boston Scientific Corporation<br>KURIBARA MEDICAL INSTRUMENTS<br>Otsuka Pharmaceutical Co., Ltd.<br>Medtronic Japan Co., Ltd.<br>Japan Lifeline Co.,Ltd. | | | Bayer Yakuhin, Ltd.<br>Bristol-Myers Squibb<br>Daiichi Sankyo Company, Limited | |
| Members:<br>Hiroyoshi Yokoi | | | | Philips Japan, Ltd.<br>MSD K.K.<br>Amgen Astellas BioPharma K.K.<br>Astellas Pharma Inc.<br>AstraZeneca K.K.<br>Abbott Vascular Japan Co., Ltd.<br>Cardinal Health Japan<br>Sanofi K.K.<br>TERUMO CORPORATION<br>HeartFlow Japan G.K.<br>Bayer Yakuhin, Ltd.<br>Boston Scientific Corporation<br>Otsuka Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Biosensors Japan Co., Ltd.<br>Nihon Medi-Physics Co.,Ltd.<br>Medtronic Japan Co., Ltd.<br>Takeda Pharmaceutical Company Limited | | | Daiichi Sankyo Company, Limited | | | | | |
| Members:<br>Kunihiro Yoshioka | | | | | | Bayer Yakuhin, Ltd. | | | | | | |
| Members:<br>Masafumi Watanabe | | | | Bayer Yakuhin, Ltd.<br>Otsuka Pharmaceutical Co., Ltd.<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Daiichi Sankyo Company, Limited | | | Astellas Pharma Inc.<br>Bayer Yakuhin, Ltd.<br>Ono Pharmaceutical Co., Ltd.<br>Chugai Pharmaceutical Co.,Ltd.<br>Medtronic Japan Co., Ltd. | | | | | |

| Author | Potential COI of the participant | | | | | | | | | Potential COI of the marital partner, firstdegree family members, or those who share income and property | Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Employer/ leadership position (private company) | Stake-holder | Patent royalty | Honorarium | Payment for manuscripts | Research grant | Scholarship (educational) grant | Endowed chair | Other rewards | | Research grant | Scholarship (educational) grant |
| Collaborators: Koichi Kaikita | | | | Bayer Yakuhin, Ltd.<br>Daiichi Sankyo Company, Limited | | SBI Pharmaceuticals Co., Ltd.<br>Novartis Pharma K.K.<br>Bayer Yakuhin, Ltd. (contracted research)<br>Bayer Yakuhin, Ltd. (industry-university joint research)<br>Daiichi Sankyo Company, Limited | | | | | | |
| Collaborators: Tokuo Kasai | | | | | | | Nihon Medi-Physics Co.,Ltd. | | | | | |
| Collaborators: Eri Kato | | | | AstraZeneca K.K.<br>Daiichi Sankyo Company, Limited | | | | | | | | Boston Scientific Corporation |
| Collaborators: Masaaki Kawashiri | | | | Amgen Astellas BioPharma K.K.<br>Astellas Pharma Inc.<br>Sanofi K.K. | Amgen Astellas BioPharma K.K. | | | | | | | |
| Collaborators: Keisuke Kiso | | | | Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM Toyama Chemical Co., Ltd. | | | | | | | | |
| Collaborators: Kakuya Kitagawa | | | | | | | | Siemens Healthcare K.K. | | | | |
| Collaborators: Tomonari Kiriyama | | | Nihon Medi-Physics Co.,Ltd. | Nihon Medi-Physics Co.,Ltd. | | | | | | | | Eisai Co., Ltd.<br>TERUMO LIFE SCIENCE FOUNDATION<br>Daiichi Sankyo Company, Limited<br>Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM RI Pharma Co., Ltd. |
| Collaborators: Teruyoshi Kume | | | | Abbott Vascular Japan Co., Ltd.<br>TERUMO CORPORATION | | | | | | | | Astellas Pharma Inc.<br>Abbott Vascular Japan Co., Ltd.<br>TERUMO CORPORATION<br>Goodman Co.,LTD. |
| Collaborators: Masami Kosuge | | | | Daiichi Sankyo Company, Limited | | | | | | | | |
| Collaborators: Eitaro Kodani | | | | Bristol-Myers Squibb<br>Ono Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited | | | | | | | | |
| Collaborators: Yasutsugu Shiono | | | | Philips Japan, Ltd.<br>Abbott Vascular Japan Co., Ltd.<br>VOLCANO JAPAN Co., Ltd. | | | | | | | Infraredx, Inc. | ACIST Medical Systems<br>Astellas Pharma Inc.<br>Abbott Vascular Japan Co., Ltd.<br>St. Jude Medical Japan Co., Ltd.<br>HeartFlow Japan G.K.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Daiichi Sankyo Company, Limited |
| Collaborators: Hiroki Shiomi | | | | | | | | | | | EP-CRSU Co., Ltd.<br>IQVIA Services Japan K.K.<br>Otsuka Pharmaceutical Co., Ltd.<br>EPS Corporation. | Astellas Pharma Inc.<br>MID,Inc.<br>Boston Scientific Corporation<br>Otsuka Pharmaceutical Co., Ltd.<br>Sumitomo Dainippon Pharma Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Nippon Boehringer Ingelheim Co., Ltd.<br>Takeda Pharmaceutical Company Limited |

| Author | Potential COI of the participant | | | | | | | | | Potential COI of the marital partner, firstdegree family members, or those who share income and property | Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Employer/ leadership position (private company) | Stake-holder | Patent royalty | Honorarium | Payment for manuscripts | Research grant | Scholarship (educational) grant | Endowed chair | Other rewards | | Research grant | Scholarship (educational) grant |
| Collaborators: Masaaki Takeuchi | | | | | | | | | | | | GE Healthcare<br>Wako Pure Chemical Industries, Ltd.<br>SEKISUI MEDICAL CO., LTD.<br>Roche Diagnostics K.K.<br>Abbott Japan LLC<br>Beckman Coulter, Inc. |
| Collaborators: Nobuhiro Tanaka | | | | Abbott Vascular Japan Co., Ltd.<br>St. Jude Medical Japan Co., Ltd.<br>Boston Scientific Corporation<br>VOLCANO JAPAN Co., Ltd.<br>Daiichi Sankyo Company, Limited | | | | | | | | |
| Collaborators: Ryoichi Tanaka | | | | | | Japan Academic Research Forum | | | | | | |
| Collaborators: Akihiro Nomura | CureApp, Inc. | | | | | | | | | | | |
| Collaborators: Takafumi Hiro | | | | | | | | Boston Scientific Corporation | | | | |
| Collaborators: Daisuke Fukamachi | | | | Sanofi K.K. | | Daiichi Sankyo Company, Limited | | | | | | |
| Collaborators: Hitoshi Matsuo | | | | Abbott Vascular Japan Co., Ltd.<br>Boston Scientific Corporation<br>Philips Japan, Ltd.<br>Philips Volcano<br>Amgen Astellas BioPharma K.K.<br>KANEKA CORPORATION<br>Daiichi Sankyo Company, Limited<br>Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM RI Pharma Co., Ltd. | | | | | | | |
| Collaborators: Naoya Matsumoto | | | | Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM Toyama Chemical Co., Ltd. | | | FUJIFILM Toyama Chemical Co., Ltd. | | | | | |
| Collaborators: Katsumi Miyauchi | | | | MSD K.K.<br>Astellas Pharma Inc.<br>Amgen Astellas BioPharma K.K.<br>Sanofi K.K.<br>Bayer Yakuhin, Ltd.<br>Bristol-Myers Squibb<br>Boehringer Ingelheim GmbH<br>Nippon Boehringer Ingelheim Co ., Ltd.<br>Daiichi Sankyo Company, Limited<br>Takeda Pharmaceutical Company Limited | | | | | | | | |
| Collaborators: Masao Miyagawa | | | | Nihon Medi-Physics Co.,Ltd.<br>FUJIFILM RI Pharma Co., Ltd. | | | | | | | | |
| Collaborators: Yoshitake Yamada | | | | | | | The Uehara Memorial Foundation | | | | | |
| Collaborators: Tetsu Watanabe | | | | | | | Daiichi Sankyo Company, Limited | | | | | Pfizer Japan Inc.<br>Astellas Pharma Inc. |
| Independent Assessment Committee: Yukio Ozaki | | | | | | | Daiichi Sankyo Company, Limited<br>Takeda Pharmaceutical Company Limited<br>Sumitomo Dainippon Pharma Co., Ltd. | | | | | |
| Independent Assessment Committee: Shun Kohsaka | | | | AstraZeneca K.K.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Bristol-Myers Squibb | | Bayer Yakuhin, Ltd.<br>Daiichi Sankyo Company, Limited | | | | | | |

| Author | Potential COI of the participant | | | | | | | | | Potential COI of the marital partner, firstdegree family members, or those who share income and property | Potential COI of the head of the organization/department to which the participant belongs (when the participant is in the position of cooperative research with the head of the organization/department) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Employer/ leadership position (private company) | Stake-holder | Patent royalty | Honorarium | Payment for manuscripts | Research grant | Scholarship (educational) grant | Endowed chair | Other rewards | | Research grant | Scholarship (educational) grant |
| Independent Assessment Committee: Wataru Shimizu | | | | Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Bristol-Myers Squibb<br>Boehringer Ingelheim GmbH<br>Ono Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Nippon Boehringer Ingelheim Co., Ltd. | | | Astellas Pharma Inc.<br>Eisai Co., Ltd.<br>St. Jude Medical Japan Co., Ltd.<br>Novartis Pharma K.K.<br>Bayer Yakuhin, Ltd.<br>Pfizer Japan Inc.<br>Bristol-Myers Squibb<br>Boehringer Ingelheim GmbH<br>Ono Pharmaceutical Co., Ltd.<br>Otsuka Pharmaceutical Co., Ltd.<br>Daiichi Sankyo Company, Limited<br>Mitsubishi Tanabe Pharma Corporation<br>Nippon Boehringer Ingelheim Co., Ltd. | | | | | |
| Independent Assessment Committee: Satoshi Yasuda | | | | Bayer Yakuhin, Ltd.<br>Bristol-Myers Squibb<br>Takeda Pharmaceutical Company Limited<br>Sanofi K.K.<br>AstraZeneca K.K.<br>Daiichi Sankyo Company, Limited | | IQVIA Services Japan K.K.<br>JSR Corporation<br>Actelion Pharmaceuticals Japan Ltd.<br>Abbott Vascular Japan Co., Ltd.<br>Quintiles Transnational Japan k.k.<br>TERUMO CORPORATION<br>Bayer Yakuhin, Ltd.<br>Takeda Pharmaceutical Company Limited | Bayer Yakuhin, Ltd.<br>Takeda Pharmaceutical Company Limited<br>Daiichi Sankyo Company, Limited | | | | | |
| Independent Assessment Committee: Hideaki Yoshino | | | | | | | Takeda Pharmaceutical Company Limited | | | | | |

Notation of corporation is omitted.
No potential COI for the following members.
Members: Nobusada Funabashi
Members: Teruhito Mochizuki
Members: Masaru Miura
Collaborators: Toshihiko Asanuma
Collaborators: Yuuichi Ishikawa
Collaborators: Takahiro Ohara
Collaborators: Hiroshi Kamiyama
Collaborators: Teruhito Kido
Collaborators: Toshio Kinoshita
Collaborators: Akira Kurata
Collaborators: Satoshi Kurisu
Collaborators: Akira Sato
Collaborators: Junichi Taki
Collaborators: Atsushi Tanaka
Collaborators: Takuya Nakahashi
Collaborators: Takehiro Nakahara
Collaborators: Akiyoshi Hashimoto
Collaborators: Kenshi Hayashi
Collaborators: Masahiro Higashi
Collaborators: Keiichiro Yoshinaga
Collaborators: Hideki Wada